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Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 356 595
A1

(2)

EUROPEAN PATENT APPLICATION

(21) Application number: 88402205.4

(51) Int. Cl.⁵: C07K 5/02 , C07K 5/06 ,
C07K 5/08 , C07K 5/10 ,
A61K 37/00

(22) Date of filing: 01.09.88

(43) Date of publication of application:
07.03.90 Bulletin 90/10

(54) Designated Contracting States:
FR

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(54) Novel peptidase inhibitors.

(57) This invention relates to analogs of peptidase substrates in which the nitrogen atom of the scissile amide bond of a partial retropeptide analog of the substrate has been replaced by a difluoromethylene moiety. These peptidase substrate analogs provide specific enzyme inhibitors for a variety of proteases, the inhibition of which exert valuable pharmacological activities and therefore have useful physiological consequences in a variety of disease states.

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NOVEL PEPTIDASE INHIBITORS

This invention relates to protease enzyme inhibitors useful for a variety of physiological end-use applications.

In its broad aspects, this invention relates to analogs of peptidase substrates in which the nitrogen atom of the scissile amide bond of a partial retropeptide analog of the substrate has been replaced by a difluoromethylene moiety. These peptidase substrate analogs provide specific enzyme inhibitors for a variety of proteases, the inhibition of which exert valuable pharmacological activities and therefore have useful physiological consequences in a variety of disease states.

In its more specific aspects, this invention relates to activated electrophilic ketone retroamide analogs of certain peptidase substrates which are useful in inhibiting serine-, thiol-, carboxylic acid- and metallo-dependent proteolytic enzymes, the inhibition of which will have useful physiological consequences in a variety of disease states.

Still more specifically, this invention relates to activated electrophilic ketone retroamide analogs of peptidase substrates which fall within the following generic groupings characterized according to their active site dependencies. Such generic groupings are:

I. Serine Dependent Enzymes: These include such enzymes such as Elastase (human leukocyte), Cathepsin G, Thrombin, Plasmin, C-1 Esterase, C-3 Convertase, Urokinase, Plasminogen Activator, Acrosin, β -Lactamase, D-Alanine-D-Alanine Carboxypeptidase, Chymotrypsin, Trypsin and Kallikreins.

II. Thio Dependent Enzymes: Cathepsin B.

III. Carboxylic Acid Dependent Enzymes: These include such specific enzymes as Renin, Pepsin and Cathepsin D.

IV. Metallo Dependent Enzymes: These include Angiotensin Converting Enzyme, Enkephalinase, Pseudomonas Elastase and Leucine Aminopeptidase.

The contemplated peptidase inhibitors of the foregoing enzymes are selected from the generic formula

$$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ \quad I$$

the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein:

R_1 is hydrogen, an amino protecting group selected from Group K, an α -amino acid or a peptide comprised of a number of α -amino acid building blocks, each of said α -amino acid or peptide optionally bearing an amino protecting group preferably selected from Group K.

R_2 is a specific characteristic "R group" side chain of the α -amino acid building block responsible for directing the inhibitor to the active site of the enzyme.

R_3 is H, C_{1-6} straight or branched alkyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl, or is the R-group residue of an α -amino acid building block for that peptidase substrate analog.

n is an integer of 1 to 10.

R_a is a specific characteristic "R-group" side chain of an α -amino acid building block for that peptidase substrate analog, or is an ethylene moiety which when attached to the N atom of that retroamide moiety forms a 2-oxopyrrolidine moiety.

R_b is H, C_{1-6} straight or branched alkyl, or an ethylene moiety which when linked to the CH moiety of X forms a 2-oxopyrrolidine moiety.

X is H, CH, OR_7 or R_7 with R_7 being C_{1-6} straight or branched alkyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with the proviso that when X is other than CH, R_a and Q are deleted.

Q is H, C_{1-10} alkyl or aralkyl, COR_5Y , or COY with R_5 being an α -amino acid R-group or a peptide comprised of α -amino acid building blocks, and

Y is NHR_4 or OR_4 , with R_4 being H, C_{1-6} straight or branched alkyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl.

Isosteres of the compounds of formula I include those wherein (a) one or more of the α -amino residues of the R_1 and Q substituents are in their unnatural configuration (when there is a natural configuration) or (b) when the normal peptidic carbamoyl linkage is modified, such as for example, to form $-CH_2NH-$ (reduced), $-COCH_2-$ (keto), $-CH(OH)CH_2-$ (hydroxy), $-CH(NH_2)CH_2-$ (amino), $-CH_2CH_2-$ (hydrocarbon). Preferably a compound of the invention should not be in an isosteric form, particularly it is preferred that there be no modified peptidic carbamoyl group in the R_1 and Q radicals, but if there is, it is preferable to keep the isosteric modifications to a minimum.

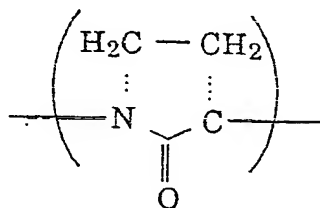
A compound of the invention may be in free form, e.g., amphoteric form, or in salt, e.g., acid addition or anionic salt, form. A compound in free form may be converted into a salt form in an art-known manner and vice-versa. Examples of salt forms are the trifluoroacetate, hydrochloride, sodium, potassium and ammonium forms.

Unless otherwise stated, the α -amino acid building blocks of these peptidase substrate analogs are preferably in their L-configuration. However, in those instances wherein there is an amide peptide bond between the CF_2 and a resulting malonyl moiety, then the α -amino acid building blocks between the CF_2 moiety and the malonyl moiety are in their D-configuration.

5 In the event n is 2 then there are two R_a moieties, (i.e., R_{a1} and R_{a2} , each of which may be the same or different), if n is 3 then there are three R_a moieties, (i.e., R_{a1} , R_{a2} and R_{a3}) each of which may be the same or different and so on for each change in the definition of n . Analogously, the X and R_b moieties would similarly be increased as n is increased, each being modified independently within the scope of their generic definitions.

10 Before further defining and/or illustrating the scope of the peptidase inhibitors embraced by formula I, it may be convenient to state some of the more basic concepts related to peptides. For example, except for proline, all of the α -amino acids found in proteins have as a common denominator a free carboxyl group and a free unsubstituted amino group on the α -carbon atom (in proline, since proline's α -amino group is substituted it is really an α -amino acid, but for convenience, it will also be spoken of as an α -amino group).

15 Additionally, each α -amino acid has a characteristic "R-group", the R-group being the side chain, or residue, attached to the α -carbon atom of the α -amino acid. For example, the R-group side chain for glycine is hydrogen, for alanine it is methyl, for valine it would be isopropyl. (Thus, throughout this specification the R_1 , R_2 , R_3 or R_5 moiety is the R-group for each indicated α -amino acid). For the specific R-groups - or side chains - of the α -amino acids reference to A.L. Lehninger's text on Biochemistry (see particularly Chapter 4) would be helpful. In those instances wherein R_a is an ethylene moiety attached to the CH group of X and to the nitrogen atom of that retroamide, that resulting 2-oxo-pyrrolidine moiety is represented by



wherein the dotted lines depict the ethylene moiety attached to the nitrogen atom of the retroamide.

As a further convenience for defining the scope of the compounds embraced by the generic concept of formula I, as well as the sub-generic concepts relating to each of the individual enzymes involved in this invention, various α -amino acids have been classified into a variety of groups which impart similar functional characteristics for each of the specific enzymes to be inhibited by the peptidase substrates of formula I. These groups are set forth in Table II and the recognized abbreviations for the α -amino acid blocks are set forth in Table I.

TABLE I

AMINO ACID	SYMBOL
Alanine	Ala
Arginine	Arg
Asparagine	Asn
Aspartic acid	Asp
Asn + Asp	Asx
Cysteine	Cys
Glutamine	Gln
Glutamic acid	Glu
Gln + Glu	Glx
Glycine	Gly
Histidine	His
Isoleucine	Ile
Leucine	Leu
Lysine	Lys
Methionine	Met
Phenylalanine	Phe
Proline	Pro
Serine	Ser
Threonine	Thr
Tryptophan	Trp
Tyrosine	Tyr
Valine	Val
Norvaline	n-Val
Norleucine	n-Leu
1-Naphthylalanine	Nal(1)
2-Indolinecarboxylic acid	Ind
Sarcosine	Sar

TABLE II

Group A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives

D: Pro, Ind

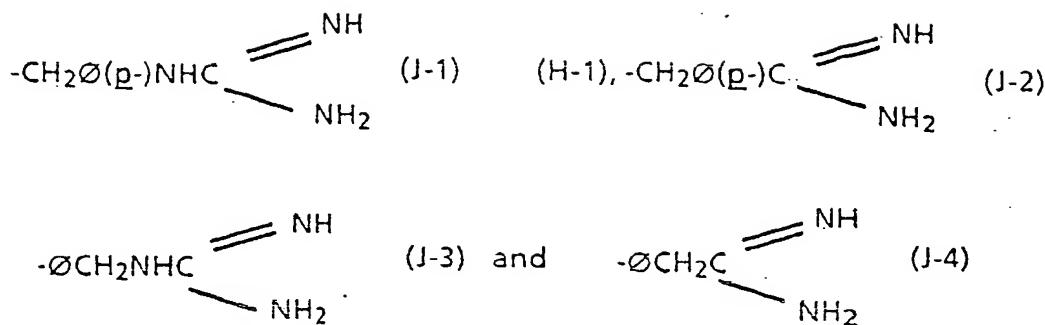
E: Ala, β -Ala, Leu, Ile, Val, n-Val, β -Val, Met, β -Valine, β -Alanine, n-Leu and n-methyl derivatives (β -representing beta)

F: Phe, Tyr, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl

derivatives

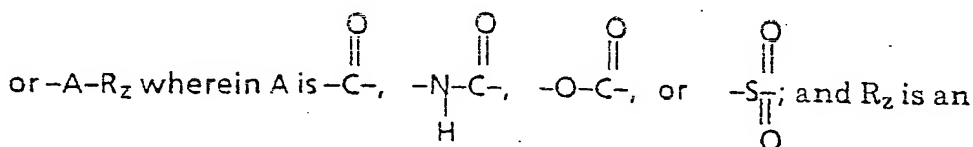
G: Gly, Sar

J:



with ϕ , of course, representing phenyl (it being understood that the bond of J1-4 is always attached to an amino acid).

20 K: Acetyl (Ac), Succinyl (suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl (AdSO₂), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)-methyl]acetyl (BNMA),



30 aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylaminocarbonyl) containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and such other terminal amino protecting groups which are functionally equivalent thereto.

In light of the foregoing, the defined compounds of formula I may also be stated as being:

40 An activated electrophilic ketone-bearing peptidase inhibitor of the formula
 $\text{R}_1\text{NHCHR}_2\text{COCF}_2\text{CHR}_3(\text{NR}_b\text{COXR}_a)_n\text{Q}$ I

the hydrates, isoteres or the pharmaceutically acceptable salts thereof wherein

R₁ is hydrogen, an amino protecting group selected from Group K, and α -amino acid or a peptide comprised a number of α -amino acid building blocks, each of said α -amino acid or peptide optionally bearing an amino protecting group preferably selected from Group K,

45 R₂ is a specific characteristic "R group" side chain of the α -amino acid building block responsible for directing the inhibitor to the active site of the enzyme,

R₃ is H, C₁₋₆ straight or branched alkyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl or 2-pyridyl-methyl, or is the R-group residue of an α -amino acid building block for that peptidase substrate analog,

n is an integer of 1 to 10,

50 R_a is a specific characteristic "R-group" side chain of an α -amino acid building block for that peptidase substrate analog, or is an ethylene moiety which when attached to the N atom of that retroamide moiety forms a 2-oxopyrrolidine moiety,

R_b is H, C₁₋₆ straight or branched alkyl, or an ethylene moiety which when linked to the CH moiety of X forms a 2-oxopyrrolidine moiety,

55 X is H, CH, OR₇ or R₇ with R₇ being C₁₋₆ straight or branched alkyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with the proviso that when X is other than CH, R_a and Q are deleted,

Q is H, C₁₋₁₀ alkyl or aralkyl, COR₅Y, or COY with R₅ being an α -amino acid R-group or a peptide

comprised of α -amino acid building blocks,

Y is NHR_4 or OR_4 , with R_4 being H, C_1 - 6 straight or branched alkyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl, wherein the said α -amino acid and peptide moieties are building blocks selected from Groups A, B, C, D, E, F, G and J, and K is a terminal amino protecting group,

members of these groups being

Group A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, and N-methyl derivatives

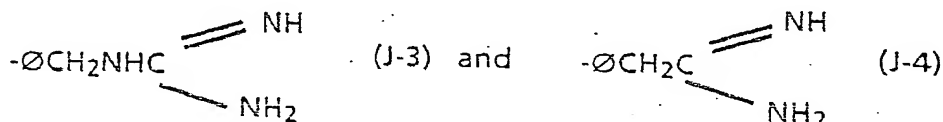
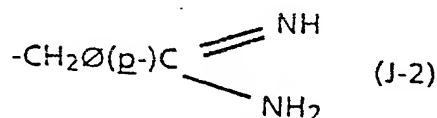
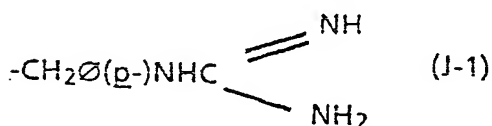
D: Pro, Ind

E: Ala, β -Ala, Leu, Ile, Val, n-Val, β -Val, Met, β -Alanine, β -Alanine, n-Leu and N-methyl derivatives

F: Phe, Tyr, Trp, Nal(1), and N-methyl derivatives

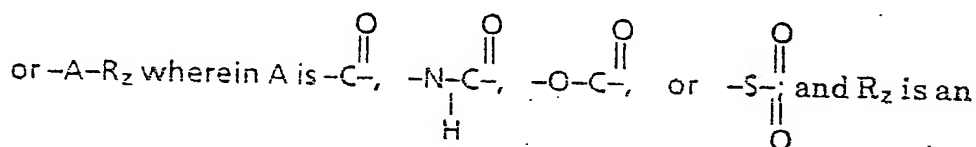
G: Gly, Sar

J:



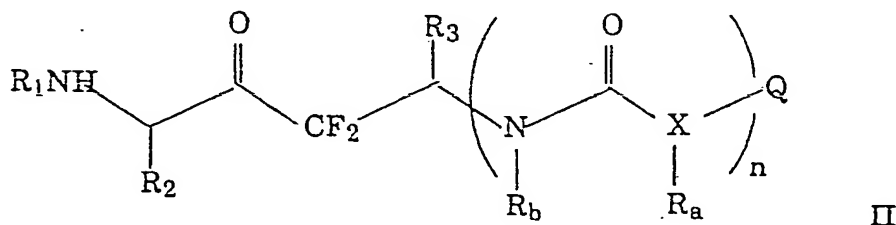
with ϕ , of course, representing phenyl (it being understood that the bond of J1-4 is always attached to an amino acid).

K: Acetyl (Ac), Succinyl (suc), Benzoyl (Bz), t-Butyloxy-carbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl (AdSO₂), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenyl-acetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)-methyl]acetyl (BNMA),



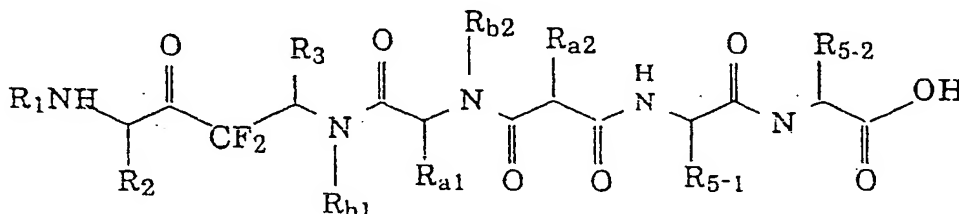
aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylaminocarbonyl) containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and such other terminal amino protecting groups which are functionally equivalent thereto.

An alternate expression of structural formula I is depicted formula II as follows:



wherein R_1 , R_2 , R_3 , R_b , R_a , n and Q are as defined for formula I. In this depiction the R_2 moiety is in the P_1 position of the peptide, the α -amino acids of the R_1 moiety would be in the $P_2 \rightarrow \dots \rightarrow P_n$ positions, n being the numeric sequence dependent upon the number of α -amino acid building blocks in that particular compound, e.g., if R_1 contained four α -amino acids it would be comprised of P_2 - P_3 - P_4 - P_5 positions with the option of a terminal amino protecting group from Group K in the P_5 moiety. The moiety containing CF_2 and R_3 is in the P_1 position of the peptide.

Formula III is used to further illustrate the type compounds embraced by formula I and to more specifically illustrate the shorthand method of naming these compounds, as follows:



This formula illustrates a compound containing two retroamide moieties, a malonyl moiety, N -substitutions for R_b moieties, X being CH , n being 2, and Q being COR_5Y with R_5 being a dipeptide moiety and Y being OH , which depiction may be written in accepted shorthand nomenclature as R_1 - R_2 - $[CF_2R_3NR_{b-1}](N-R_{b-2}-R_{a1})$ - m - R_{a2} - R_{5-1} - $R_{5-2}OH$.

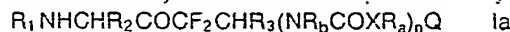
From formula III it is quite obvious that the bracketed CF_2 -retroamide inhibiting moiety is a moiety wherein the nitrogen atom of the α -amino acid has been replaced by a CF_2 radical, the R -residue remaining as defined for R_3 and the amide bond linking the two amino acids corresponding to the P_1 and P_2 positions has been reversed. Similarly, the amide bond linking the P_2 and P_3 positions has also been reversed. The brackets designate the retroamide moiety containing the CF_2 moiety, the parenthesis embracing the $NR_{b-2}-R_{a1}$ moiety indicates that it also is in a retroamide configuration and the underlined m (i.e., meta) indicates a malonyl moiety containing the R_{a-2} α -amino acid residue.

To further illustrate the shorthand nomenclature used throughout this application assume that R_1 is comprised of P_2 , P_3 , P_4 having a terminal amino protecting group so that R_1 is $-Pro-Ala-Ala-Suc-OCH_3$, R_2 is Val , R_3 is Gly , R_{b1} is ethyl, R_{a1} is H , R_{b2} is ethyl, R_{a2} is Gly , R_{5-1} is Val , R_{5-2} is Gly , then that specific compound would be written as $H_3CO-Suc-Ala-Ala-Pro-Val$;-[$CF_2GlyN-Et$]($N-EtGly$)- m - $Gly-Val-GlyOH$.

It is also to be noted that in some instances it is more convenient to designate the terminal amino protecting group as a separate P_n position of the peptide, for example, in illustrative formula III. The terminal amino protecting group would be designated as being in the P_5 position and thus R_1 would be P_2 - P_3 - P_4 - P_5 with P_5 being a protecting group of Group K. If P_4 optionally is an R group or is deleted, then quite obviously, when P_4 is deleted the protecting group of P_5 would be attached to the P_3 moiety. In those instances wherein Group K represents an $-A-R_z$ moiety, it is preferred that A represent $-C(=O)-$ and that R_z represent acylsulfonamido, particularly those wherein the acylsulfonamido contains an aryl moiety (preferably phenyl) substituted by a halogen, the preferred $-A-R_z$ moieties being 4-[(4-chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl, 4-[(4-bromophenyl)sulfonylaminocarbonyl]phenylcarbonyl and 4-[(phenylsulfonylaminocarbonyl)phenylcarbonyl] (said moieties being abbreviated as $Cl\phi$ -SAC-Bz, $Br\phi$ -SAC-Bz and ϕ -SAC-Bz, respectively).

In general and unless otherwise stated, from the CF_2 inhibiting moiety to the malonyl moiety the amino acids (or R Groups) are in their D -configuration, thereon they are in their L -configuration.

Utilizing the foregoing illustrations those compounds of formula I which are useful as inhibitors for human leukocyte elastase are represented by the formula



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R_1 is $-P_2P_3P_4P_5$ with

P_2 being α -amino acid block having an R group selected from Groups D, E and F, with proline being preferred,

P_3 is the α -amino acid blocks of Groups D, E, or lysine with isoleucine, valine or alanine being preferred,

P_4 is the α -amino acid blocks of Groups E or zero with alanine being preferred (when P_n is zero then that particular moiety does not appear in the structure, i.e., it is deleted), and

P_5 is a terminal moiety of Group K with methoxysuccinyl and CBZ and $Cl\phi$ -SAC-Bz, $Br\phi$ -SAC-Bz and ϕ -SAC-Bz being preferred.

R_2 is the R Group of Groups E and G, with nor-valine and valine being preferred,

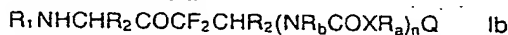
R_3 is an R Group selected from Groups E and G, with glycine and alanine being preferred,

R_a is an R Group selected from Groups E and G or is phenyl, with alanine, phenyl and glycine being preferred, with R_b , X, n and Q being as generically defined for formula I, n preferably being 1 or 2, R_b preferably being H, X preferably being CH, Q preferably being H or CONH_2 and R_5 , when present, is an α -amino acid having an R group selected from Groups E and G with alanine being preferred and then Y preferably is NH_2 .

Human leukocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Thus the peptidase substrates of formula (Ia) have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. In their end-use application the enzyme inhibitory properties of the compounds of (Ia) are readily ascertained by standard biochemical techniques well known in the art. Potential dose range for their end-use application will of course depend upon the nature and severity of the disease state as determined by the attending diagnostician with the range of 0.01 to 10 mg/kg body weight per day being useful for the aforementioned disease states with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds for this enzyme are:

$\text{H}_3\text{CO-Suc-Ala-Ala-Pro-Val-}[\text{CF}_2\text{GlyNH}]_m\text{-Gly-NH}_2$,
 $\text{H}_3\text{CO-Suc-Ala-Ile-Pro-Val-}[\text{CF}_2\text{GlyNH}]_m\text{-Ala-NH}_2$,
 $[\alpha\text{N-(AdSO}_2\text{)}-[\epsilon\text{N-2(CBZ)}]\text{-Lys-Pro-Val-}[\text{CF}_2\text{GlyNH}]_m\text{-Ala-NH}_2$,
 $[\alpha\text{N-(AdSO}_2\text{)}-[\epsilon\text{N-2(CBZ)}]\text{-Lys-Pro-Val-}[\text{CF}_2\text{GlyNH}]_m\text{-Ala-OH}$,
 $[\alpha\text{N-(AdSO}_2\text{)}-[\epsilon\text{N-2(CBZ)}]\text{-Lys-Pro-Val-}[\text{CF}_2\text{GlyNH}]_m\text{-Ala-OMe}$,
 $\text{H}_3\text{CO-Suc-Ala-Ala-Pro-Val-}[\text{CF}_2\text{GlyNH}]\text{COCH}_3$,
 $\text{CBZ-Val-Pro-Val}[\text{CF}_2\text{GlyNH}]\text{COCH}_2\text{O}$,
 $4\text{-Cl}\phi\text{-SAC-Bz-Val-Pro-Val-}[\text{CF}_2\text{GlyNH}]\text{COCH}_2\phi$,
 $4\text{-Br}\phi\text{-SAC-Bz-Val-Pro-Val-}[\text{CF}_2\text{GlyNH}]\text{COCH}_2\phi$,
 $4\text{-}\phi\text{-SAC-Bz-Val-Pro-Val-}[\text{CF}_2\text{GlyNH}]\text{COCH}_2\phi$,
 $4\text{-HOOC}\phi\text{CO-Val-Pro-Val-}[\text{CF}_2\text{GlyNH}]\text{COCH}_2\phi$,
 $4\text{-Cl}\phi\text{-SAC-Bz-Val-Pro-Val-}[\text{CF}_2\text{GlyNH}]\text{COCH}_3$.

Those compounds of formula I which are useful as inhibitors of Cathepsin G are represented by the structural formula



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R_1 is $-\text{P}_2\text{P}_3\text{P}_4\text{P}_5$ with P_2 being selected from Groups D, E, or G, with proline being preferred

P_3 is selected from Groups E or G with alanine being preferred,

P_4 is selected from Groups E, G or is deleted with alanine being preferred, the terminal α -amino acid optionally bearing a protecting group selected from Group K with succinyl or methoxy succinyl being preferred,

R_2 is selected from Groups E and F but preferably is Phe,

R_3 is as generically defined for formula I with the α -amino acid residue being selected from Groups E and G, Gly, Ala and Phe being preferred,

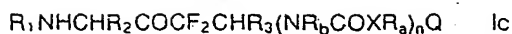
R_b , X, n and Q are as generically defined in formula I

with R_b preferably being H, n preferably being 1, Q preferably is H and R_a and R_5 are as defined for formula (Ia).

The end-use application of the compounds (Ib) inhibiting Cathepsin G is the same as for human leukocyte inhibitors, including arthritis, gout and emphysema, but also embracing the treatment of glomerulonephritis and lung infestations caused by infections in the lungs. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ib) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 to 10 mg/kg per day being preferred. Preferred compounds for formula (Ib) are:

$\text{CH}_3\text{O-Suc-Ala-Ala-Pro-Phe-}[\text{CF}_2\text{-Gly-NH}]\text{COCH}_3$,
 $\text{Suc-Ala-Ala-Pro-Phe-}[\text{CF}_2\text{-Phe-NH}]\text{COCH}_3$,
 $\text{Suc-Ala-Ala-Pro-Phe-}[\text{CF}_2\text{-Ala-NH}]\text{CO}_2\text{CH}_3$,
 $\text{Suc-Ala-Ala-Pro-Phe-}[\text{CF}_2\text{-Ala-NH}]\text{CO}_2\text{Et}$.

Those compounds of formula I which are useful as inhibitors of thrombin are represented by the formula



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R_1 is (a) $-P_2-P_3$, (b) $-P_2$ or (c) $-P_2-P_3-P_4$ wherein:

- (a) P_2 is selected from Groups D, E or F, preferably proline, P_3 is selected from Group F, each P_3 is selected from Group F, each P_3 being in the D-configuration, preferably D-Phe,
 (b) P_2 is selected from Group K but preferably is dansyl, tosyl or benzoyl,
 (c) P_2 is selected from Group E but preferably is alanine, P_3 is selected from Groups C, "G and E but preferably is serine, P_4 is selected from Groups F, G and E or is zero but preferably is Phe,
 R_2 is preferably the arginine side chain but may also be selected from Groups A and J, preferably JI,
 R_3 is as generically defined for formula I, with the residue being selected from Groups C and G with glycine and serine being preferred,
 R_a is selected from Group C or G but preferably is a glycine or serine side chain,
 R_b , n, X and Q are as generically defined for formula I,
 R_b preferably being H, X preferably being CH, and Q preferably is H or alkyl and
 R_5 is preferably the glycine amino acid residue or is a residue of an α -amino acid of Group E or D or is zero.

The compounds embraced by formula (Ic) inhibit thrombin and therefore, as in the use of heparin, the compounds may be used as the initial anticoagulant agent in thrombophlebitis and coronary thrombosis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ic) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Preferred compounds are as expressed for Cathepsin G and also include:

- H-(D)-Phe-Pro-JI-[CF₂-Gly-NH]COC₃H₇,
 H-(D)-Phe-Pro-Arg-[CF₂-Gly-NH]COC₃H₇,
 DNS-Arg-[CF₂-Gly-NH]COC₃H₇,
 H-Phe-Ser-Ala-[CF₂-Gly-NH]COC₃H₇,
 H-(D)-Phe-Pro-Lys-[CF₂-Gly-NH]COOH₃,
 Bz-J-I-[CF₂-Gly-NH]COCH₃.

The compounds of formula I which are useful as inhibitors of chymotrypsin are represented by the structural formula



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R_3 , R_a , R_b , X and Q are defined for compounds of (Ia), and

R_1 is $-P_2P_3P_4P_5$ with

- P_2 being selected from Groups D, E, with Leu being preferred, G or K with benzoyl being preferred,
 P_3 is selected from Groups E or G or K, with acetyl being preferred, or is deleted, with alanine being preferred,
 P_4 is selected from Groups E or G or K or is deleted, with alanine being preferred,
 P_5 is selected from Group K with succinyl being preferred or is deleted, and
 R_2 is selected from Groups E and F but preferably is Phe or Tyr.

The end-use application of the compounds (Id) inhibiting chymotrypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Id) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. Preferred compounds are as expressed for Cathepsin G and also include:

- Bz-Phe-[CF₂-Gly-NH]COCH₃,
 Bz-Phe-[CF₂-Gly-NH]COOMe,
 Bz-Tyr-[CF₂-Gly-NH]COCH₃,
 Bz-Tyr-[CF₂-Gly-NH]COOMe,
 Ac-Leu-Phe-[CF₂GLYNH]COCH₃.

The compounds of formula I which are useful as inhibitors of trypsin are represented by the structural formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ 1e

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R_2 , R_3 , R_a , R_b , n , X and Q generically are as defined in (1c),

R_1 is selected from (a) $-P_2-P_3$, (b) $-P_2$ or (c) $-P_2-P_3-P_4$ with

(a) P_2 is selected from Groups "E or F but is preferably proline or alanine, P_3 is selected from Group F, (each being in the D configuration) but preferably is (d) -Phe,

(b) P_2 is selected from Group K but preferably is dansyl, tosyl or benzoyl,

(c) P_2 is selected from Group D or E but preferably is proline or alanine, P_3 is selected from Groups G and E but preferably is serine, P_4 is selected from Groups G and E or is zero but preferably is Phe.

The end-use application of the compounds (1e) inhibiting trypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (1e) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds useful for inhibiting trypsin are the same as for the inhibitors of thrombin.

The compounds of formula I which are useful as inhibitors of plasmin are represented by the structural formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ 1f

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein R_3 , R_a , R_b , X , n and Q are as defined in formula I:

R_1 is $-P_2P_3P_4$ with

P_2 being selected from Group E or F but preferably is Ala or Phe,

P_3 is selected from Groups B, F or K but preferably is Glu or acetyl, and

P_4 is selected from Group K or is deleted but preferably is dansyl,

R_2 is selected from Groups A and J but preferably is lysine or J-I, and

n preferably is one and

R_b preferably is H.

The compounds embraced by formula (1f) inhibit plasmin and are therefore antiproliferative agents useful in treating excessive cell growth, particularly in the treatment of benign prostatic hypertrophy and prostatic carcinoma, and in the treatment of psoriasis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (1f) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 to 10 mg/kg per day being preferred. The preferred compounds are:

DNS-Glu-Phe-Lys[CF₂-Gly-NH]_m-Ala-OH,

DNS-Glu-Phe-Lys[CF₂-Gly-NH]_m-Ala-NH₂,

DNS-Glu-Phe-Lys[CF₂-Gly-NH]_m-Ala-OC₁₋₄-Alkyl,

Ac-Ala-J-I[CF₂-Gly-NH]COCH₃,

Ac-Ala-Lys-[CF₂-Gly-NH]COCH₃.

The compounds of formula I which are useful as inhibitors of C₁-esterase are represented by the structural formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ 1g

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein

Q , R_3 , R_b and X are defined in formula I, with the R-group of R_3 selected from Group E or G,

R_1 generically is $-P_2-P_3$ with P_2 being selected from Groups E, G, D, C, F, A or B with Ala being preferred, and

P_3 is selected from Group K with CBZ or acetyl being preferred,

R_2 is selected from Groups A and J, but preferably is Arg or J-I,

R_a is selected from Group E or G, preferably Gly,

n preferably is one, and

R_b preferably is H.

The compounds embraced by formula (1g) inhibit C₁-esterase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the

compounds of (I_g) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds are:

CBZ-Ala-Arg-[CF₂-Gly-NH]COCH₃,
 CBZ-Ala-Arg-[CF₂-Gly-NH]COOC₁₋₄-Alkyl,
 CBZ-Ala-Arg-[CF₂-Gly-NH]m-Gly-NH₂,
 Ac-Ala-J-I[CF₂-Gly-NH]COCH₃.

The compounds of formula I which are useful as inhibitors of C₃-convertase are represented by the formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ (I_h)

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein generically R_b, X, n and Q are as defined in formula I,

R₁ is -P₂P₃P₄ with

P₂ being selected from Groups E or F, with Ala being preferred,

P₃ is selected from Groups E or F with Leu being preferred, and

P₄ is selected from Group K with Bz being preferred,

R₂ is selected from Groups A or J, with Arg being preferred,

R₃ is selected from Groups E or G, with Gly being preferred,

R₅ is zero and

Y preferably is NH₂,

R_a is selected from Group "E" but preferably is Ala,

R_b preferably is H.

The compounds embraced by formula (I_h) inhibit C₃-convertase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (I_h) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds are:

Bz-Leu-Ala-Arg-[CF₂-Gly-NH]COCH₃,

Bz-Leu-Ala-Arg-[CF₂-Gly-NH]COOC₁₋₄-Alkyl,

Bz-Leu-Ala-Arg-[CF₂-Gly-NH]COO-Benzyl,

Bz-Leu-Ala-Arg-[CF₂-Gly-NH]m-Ala-NH₂.

The compounds of formula I which are useful as inhibitors of Urokinase are represented by the formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ (I_i)

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R₃, R_a, R_b, X, n and Q are as defined in formula I,

R₁ generically is -P₂P₃ with

P₂ being selected from Groups E and G with Ala and Gly being preferred, and

P₃ is selected from Group B with Glu being preferred,

R₂ is selected from Groups A and J with Arg being preferred, and the R-group of R₃ and R_a being selected

from Group E, each preferably being Ala and

Y preferably being NH₂, and

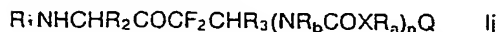
R_b preferably is H.

The compounds embraced by formula (I_i) inhibit Urokinase and therefore are useful in treating excessive cell growth disease states. As such compounds are useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, the treatment of psoriasis, and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (I_i) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds are:

K-Glu-Gly-Arg-[CF₂-Ala-NH]m-Ala-NH₂,

K-Glu-Gly-Arg-[CF₂-Ala-NH](Ala)CHO,
 K-Glu-Gly-Arg-[CF₂-Ala-NH](Ala)CO₂CH₃,
 K-Glu-Gly-(p-gua)-Phe-[CF₂-Ala-NH](Ala)H,
 (K being a protecting group).

5 The compounds of formula I which are useful as inhibitors of plasminogen activator are represented by the structural formula



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
 R₃, R_a, R_b, X, n and Q are as defined in formula I,

10 R₁ generically is -P₂P₃P₄ wherein

P₂ is Gly,

P₃ is selected from Group B with Glu being preferred, and

P₄ preferably is dansyl but also selected from Group K, and

R₂ is selected from Groups A and J with Arg being preferred.

15 Preferred compounds are:

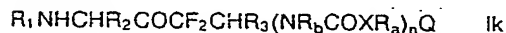
DNS-Glu-Gly-Arg-[CF₂-Ala-NH](Ala)CHO,

DNS-Glu-Gly-(p-gua)-Phe-[CF₂-Ala-NH](Ala)H,

DNS-Glu-Gly-Arg-[CF₂-Ala-NH]m-Ala-NH₂.

The compounds embraced by formula (Ij) inhibit plasminogen activator and therefore are useful in
 20 treating excessive cell growth disease states such as, for example, being useful in the treatment of benign
 prostatic hypertrophy and prostatic carcinoma, in the treatment of psoriasis and in their use as aborti-
 ficants. For their end-use application, the potency and other biochemical parameters of the enzyme
 inhibiting characteristics of the compounds of (Ij) are readily ascertained by standard biochemical tech-
 niques well known in the art. Actual dose ranges for their specific end-use application will, of course,
 25 depend upon the nature and severity of the disease state of the patient or animal to be treated as
 determined by the attending diagnostician. It is to be expected that the general end-use application dose
 range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per
 day being preferred.

The compounds of formula I which are useful as inhibitors of acrosin are represented by the structural
 30 formula



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
 R₃, R_a, R_b, X, n and Q are as defined in formula I,

R₁ is -P₂P₃P₄ with

35 P₂ being selected from Group E or K with Leu or benzoyl being preferred,

P₃ is selected from Group E with Leu being preferred or is deleted,

P₄ is selected from Group K with Boc being preferred or is deleted,

R₂ is selected from Groups A and J with Arg and J-I being preferred, the R-groups of R₃ being selected
 40 from Group E or G, and

n preferably is one.

The preferred compounds are:

Boc-Leu-Leu-Arg-[CF₂-Gly-NH](Ala)CHO,

Boc-Leu-Leu-p-gua-Phe-[CF₂-Gly-NH]m-Ala-NH₂,

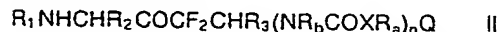
Boc-Leu-Leu-Arg-[CF₂-Gly-NH]m-Ala-OH,

45 Boc-Leu-Leu-Arg-[CF₂-Gly-NH]COCH₃,

BZ-J-I-[CF₂-Gly-NH]COCH₃.

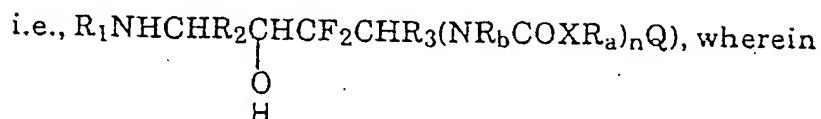
The compounds of formula (Ik) are acrosin inhibitors and therefore are useful as anti-fertility agents in
 that they possess the characteristics of preventing sperm from penetrating an otherwise fertilizable egg. For
 their end-use application, the potency and other biochemical parameters of the enzyme inhibiting char-
 50 acteristics of the compounds of (Ik) are readily ascertained by standard biochemical techniques well known
 in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the state of
 the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that
 the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective
 therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

55 The compounds of formula I which are useful as inhibitors of β -lactamase are represented by the
 structural formula



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, with the proviso that the P1

carbonyl moiety may exist in its chemically reduced form



R_1 is P_2 ,

P_2 being selected from Group K with $COCH_2\phi$ and Bz being preferred,

R_2 is selected from Groups E, G and C with glycine being preferred, and

R_3 , R_a , R_b , X, n and Q being as defined in formula I, with the R groups of R_3 being selected from Group E or G, and

n preferably is one.

The preferred compounds are:

$\phi CH_2CONHCH_2CO[CF_2-Gly-NH]COCH_3$,

$\phi CH_2CONHCH_2CHOH[CF_2-Gly-NH]COCH_3$.

The compounds embraced by formula (II) inhibit β -lactamase and therefore are useful in the potentiation of antibacterial agents, particularly the β -lactam antibacterials. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (II) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of D-Ala-D-Ala carboxypeptidase are represented by the structural formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ Im

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R_1 is P_2 - P_3 with

P_2 being N ϵ -Ac-Lys or is selected from Groups E and C with N ϵ -Ac-Lys being preferred,

P_3 is selected from Group K with Ac being preferred,

R_2 is D-Ala, and

R_3 , R_a , R_b , X and Q are as defined in formula I, with the R-group of R_3 being selected from Group E with D-Ala being preferred,

n preferably is one,

R_b being preferably H,

R_5 preferably is deleted and

Y preferably is OH.

The preferred compounds are:

(N α,ϵ)-di-Ac-Lys-D-Ala[CF₂-Ala-NH]CHO,

(N α,ϵ)-di-Ac-Lys-D-Ala[CF₂-Ala-NH]_m-Gly-OH.

The compounds embraced by formula (Im) are antibacterial agents particularly useful against gram negative organisms. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Im) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of Cathepsin B are represented by the structural formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ In

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R_1 is (a) - P_2 - P_3 or (b) - P_2 - P_3 - P_4 wherein

(a) P_2 is selected from Groups E and F with Phe being preferred and,

P_3 is selected from Group K with CBZ being preferred,

(b) P_2 is selected from Groups E and F with Leu being preferred,

P_3 being selected from Groups E and F with Leu being preferred, and

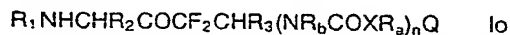
P₄ is selected from Group K with Ac being preferred,
 R₂ is selected from Groups A and J or ThrOCH₂φ, with Arg being preferred, and
 R₃, R_a, R_b, X, n and Q are as defined in formula I.

The preferred compounds are:

- 5 CBZ-Phe-J-I-[CF₂-Gly-NH]COCH₃,
 Ac-Leu-Leu-J-I-[CF₂-Gly-NH]m-Gly-OH,
 Ac-Leu-Leu-Arg[CF₂-Gly-NH]m-Gly-OH.

The compounds embraced by formula (In) inhibit Cathepsin B and therefore are useful in treating excessive cell growth disease states such as, for example, being useful in treating benign prostate hypertrophy, prostatic carcinoma, in treating psoriasis and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (In) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of renin are represented by the structural formula



and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, with the proviso that the carbonyl moiety of P-1 may exist in its chemically reduced form, (i.e., R₁NHCH(R₂)CHOHCF₂CH(R₃)-NR_bCOXR_a)_nQ) wherein R₁ generically is -P₂P₃P₄P₅P₆ wherein

P₂ is selected from Groups E, C or F with His, n-Val, (3-pyrazolyl)Ala or (4-pyrimidinyl)Ala, and n-Leu being preferred,

P₃ is selected from Groups E or F or is deleted with Phe or O-Methyl Tyrosine being preferred,

P₄ is selected from Groups E, D, F or is deleted with Pro, β-Ala or β-Val being preferred,

P₅ is selected from Groups E, C, F or is deleted with His being preferred, and

P₆ is selected from Group K with Boc, CBZ or Tba being preferred, or being BNMA when P₃, P₄, P₅ are deleted, or when P₄ is β-valine or β-alanine, P₅ and P₆ are deleted.

R₂ is selected from Groups E or F or is cyclohexylmethylene with Leu or cyclohexylmethylene being preferred, and

R₃, R_a, R_b, X, n and Q are as defined in formula I with

R_a preferably being selected from Groups G, E, or F,

R_b preferably being H,

X preferably being CH, and

R₅ is (a) P_x or (b) P_x-P_{x+1} (x being the appropriate number for that particular p' position of any given particular compound with P_x being selected from Groups E, C or F or is deleted, with His being preferred,

P_{x+1} being selected from Groups E or C or is deleted, or is Lys with Lys being preferred, and

Y preferably is OH, or NHTR₄ with R₄ preferably being H.

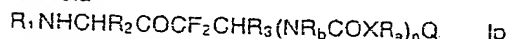
The preferred compounds are:

- 40 CBZ-Na1(1)-His-Leu[CF₂-Gly-NH](Val)CO-Benzyl,
 CBZ-Na1(1)-His-Leu[CF₂-Gly-NH]m-Val-NH-Benzyl,
 CBZ-Phe-His-Leu-[CF₂-Gly-NH]m-Val-NH-Benzyl,
 BOC-Phe-n-Val-Leu-[CF₂-Gly-NH]m-Val-NH-Benzyl,
 45 CBZ-Phe-n-Val-Leu-[CF₂-Gly-NH]m-Val-NH-Benzyl, BOC-Phe-n-Val-Leu-[CF₂-Gly-NH]m-Ile-NH-2-pyridyl-methyl,
 BOC-His-Pro-Phe-His-Leu[CF₂-Val-NH]m-Ile-His-OH,
 BOC-His-Pro-Phe-His-Leu[CF₂-Val-NH]m-Ile-His-NH₂,
 CBZ-Phe-His-"CHM"-[CF₂-Gly-NH](Val)CO-benzyl,
 50 CBZ-Phe-His-"CHM"-[CF₂-Gly-NH]m-Ile-NH-2-pyridylmethyl,
 BOC-Phe-n-Val-Leu[CF₂-Gly-NH](Val)CO-Benzyl,
 CBZ-His-Leu-[CF₂-Gly-NH]m-Val-NH-benzyl,
 BOC-Phe-His-Leu[CF₂-Gly-NH]m-Val-NH-benzyl,
 BOC-Phe-n-Val-Leu[CF₂-Gly-NH]m-Ala-NH-benzyl,
 55 BOC-Phe-n-Val-Leu[CF₂-Gly-NH]m-Gly-NH-benzyl,
 BOC-Phe-n-Val-Leu[CF₂-Gly-NH]Iva,
 BOC-Phe-n-Val-Leu[CF₂-Gly-NH]CO₂(-methylpropyl),
 BOC-Phe-n-Val-"CHM"-[CF₂-Gly-NH]m-Val-NH-benzyl,

- BOC-Phe-n-Val-"CHM"-[CF₂-Gly-NH]Iva,
 BOC-Phe-n-Val-Leu[CF₂-Gly-NH]CO[1-(1-methylpropyl)-4-phenylbutyl],
 BOC-(O-Me)Tyr-n-Val-"CHM"-[CF₂-Val-NH]Iva,
 BOC-Phe-(3-pyrazolyl)Ala-"CHM"-[CF₂-Val-NH]Iva,
 5 Tba-(O-Me)Tyr-n-Val-"CHM"-[CF₂-Val-NH]Iva,
 Tba-(O-Me)Tyr-(4-pyrimidinyl)Ala-"CHM"[CF₂-Val-NH]Iva,
 H-β-Ala-(OMe)Tyr-n-Val-"CHM"[CF₂-Gly-NH]Iva,
 H-β-Ala-(OMe)Tyr-n-Val-"CHM"[CF₂-Val-NH]Iva,
 H-β-Val-(OMe)Tyr-n-Val-"CHM"[CF₂-Gly-NH]Iva,
 10 H-β-Val-(OMe)Tyr-His-"CHM"[CF₂-Gly-NH]Iva,
 H-β-Ala-(OMe)Tyr-His-"CHM"[CF₂-Gly-NH]Iva,
 with "CHM" being an abbreviation for cyclohexylmethylene.

The compounds of formula (Io) inhibit renin and therefore are used as antihypertensive agents useful in treating hypertension. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Io) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of pepsin are represented by the structural formula



- and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, with the proviso that the P-1 carbonyl moiety may exist in its chemically reduced form (i.e., R₁NHCHR₂CHOHCF₂CHR₃(NR_bCOXR_a)_nQ), wherein R₃, R_a, R_b, X, n and Q are as defined in formula I,

R₁ is -P₂P₃P₄ with

P₂ being selected from Groups E or F with Val being preferred,

P₃ is selected from Groups E or F with Val being preferred or is deleted and

- 30 P₄ is selected from Group K, preferably Iva, and

R₂ is selected from Groups E and F with Leu being preferred,

Y is preferably -NH(CH₂)₂CH(CH₃)₂(Iaa) or -NHCH₂(CH₃)₂ (with (Iaa) being isoamylamide) and

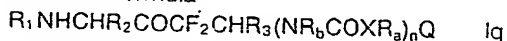
R₃ preferably is Gly.

The preferred compounds are:

- 35 Iva-Val-Leu[CF₂-Gly-NH](Ala)Iva,
 Iva-Val-Val-Leu[CF₂-Gly-NH](Ala)Iva,
 Iva-Val-Leu[CF₂-Gly-NH]m-Ala-Iaa,
 Iva-Val-Val-Leu[CF₂-Gly-NH]m-Ala-Iaa.

- The compounds of formula (Ip) inhibit pepsin and therefore exert an antiulcer effect useful in the treatment and prevention of ulcers. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ip) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of Cathepsin D are represented by the structural formula



- 50 and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein R₃, R_a, R_b, n, X and Q are as defined in formula I,

R₁ generically is -P₂P₃P₄ with

P₂ being selected from Groups E and F, with Val or Ala being preferred,

P₃ is selected from Groups E and F or is deleted with Val being preferred, and

- 55 P₄ is selected from Group K with CBZ being preferred, and

R₂ is selected from Groups E and F, with Phe being preferred,

Y preferably is -NH(CH₂)₂CH(CH₃)₂(Iaa) or -NHCH₂CH(CH₃)₂,

X preferably is CH,

R_a preferably is Ala.

n preferably is 1 or 2.

Q preferably is H or COY or COR_5Y with

R_5 preferably being Phe.

5 The preferred compounds are:

CBZ-Val-Val-Phe-[CF₂-Phe-NH](Ala)Iva,

CBZ-Val-Val-Phe-[CF₂-Phe-NH]m-Ala-NHCH₂CH(CH₃)₂,

Iva-Val-Ala-Phe[CF₂-Gly-NH](Ala)Iva,

Iva-Val-Phe[CF₂-Gly-NH]m-Ala-Phe-OCH₃.

10 As inhibitors of Cathepsin D the compounds of formula (Iq) are useful for the same end-use applications set forth for human leukocyte elastase inhibitors (Ia) and are also useful as antidemyelinating agents useful to prevent and arrest nerve tissue damage. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (In) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use
15 application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of angiotensin converting enzyme (ACE) are represented by the structural formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ Ir

and the hydrates, isoteres or the pharmaceutically acceptable salts thereof, wherein

R_3 , R_a , R_b , X , n and Q are as defined in formula I,

R_1 is selected from Group K with Bz being preferred,

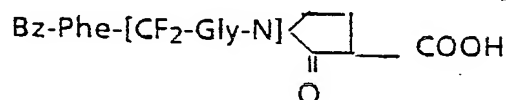
25 R_2 is selected from Groups E, F and G with Phe being preferred.

The preferred compounds are:

Bz-Phe-[CF₂-Gly-NCH₃]m-Gly-OH,

Bz-Phe-[CF₂-Gly-NH]m-Gly-OH,

30



35

Bz-Phe-[CF₂-Ala-NH]m-Gly-OH.

The compounds of formula (Ir) inhibit ACE and are therefore useful as antihypertensives useful in treating hypertension. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ir) are readily ascertained by standard biochemical
40 techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

45 The compounds of formula I which are useful as inhibitors of enkephalinase are represented by the structural formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ Is

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R_1 generically is -P₂P₃, with

50 P₂ being Gly and

P₃ being selected from Group F or is deleted with Tyr being preferred, and

R_2 is Gly, with

R_3 , R_a , R_b , n , and Q are as defined in I with

R_a preferably being methionine or leucine, and

55 Q preferably is COY with

Y being OH, and

n is preferably one.

The preferred compounds are:

H-Tyr-Gly-Gly[CF₂-Phe-NH]m-Met-OH,
H-Tyr-Gly-Gly[CF₂-Phe-NH]m-Leu-OH.

The compounds of formula (Is) inhibit enkephalinase and therefore are useful as analgesics. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Is) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of pseudomonas elastase are represented by the structural formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ It

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R₃, R_a, R_b, X, n and Q are as defined in formula I,

R₁ is -P₂P₃ with

P₂ being selected from Group E with Ala being preferred,

P₃ is selected from Group K with MeOSuc being preferred,

R₂ is selected from Groups E and G with Ala being preferred.

The preferred compound is

MeOSuc-Ala-Ala-[CF₂-Ile-NH]m-Ala-NH₂.

The compounds of formula (It) inhibit pseudomonas elastase and therefore are useful as antibacterial agents particularly useful against infections caused by pseudomonas bacteria. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (It) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of leucine aminopeptidase are represented by the structural formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ Iu

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R₃, R_a, R_b, X, n and Q are as defined in formula I,

R₁ is hydrogen, and

R₂ is selected from Groups A, B, E, F and J with Phe, Leu, Glu and with Arg being preferred.

The preferred compounds are:

H-Leu[CF₂-Gly-NH](Ala)Iva,

H-Phe[CF₂-Gly-NH]m-Gly-OH,

H-Leu[CF₂-Ala-NH](Gly)Iva

H-Leu[CF₂-Gly-NH]m-Ala-NH-benzyl,

H-Leu[CF₂-Gly-NH]m-Val-NH-benzyl,

H-Leu[CF₂-Gly-NH](Ala)CO-benzyl.

The compounds of formula (Iu) are inhibitors of leucine amino peptidase and therefore are useful as immunostimulants useful in conjunctive therapy in the treatment with other known anticancer agents. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Iu) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

The compounds of formula I which are useful as inhibitors of kallikreins, tissue or plasma, are represented by the structural formula

$R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$ Iv

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R₃, R_a, R_b, X, n and Q are as defined in formula I,

R₁ is -P₂P₃ with

P₂ being selected from Groups E and F with Phe being preferred,

P₃ being selected from Groups C, E or F, the residues of which may be in either the D- or L-configuration, and

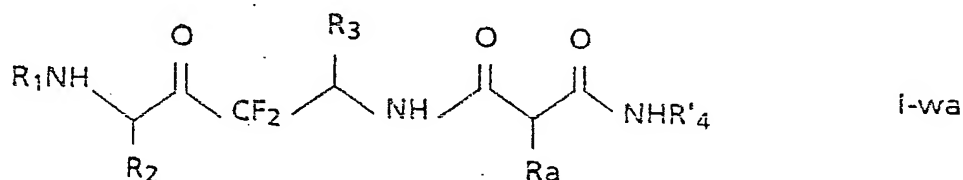
R₂ preferably is the Arg or J-1 residue.

The preferred compounds of this formula are:

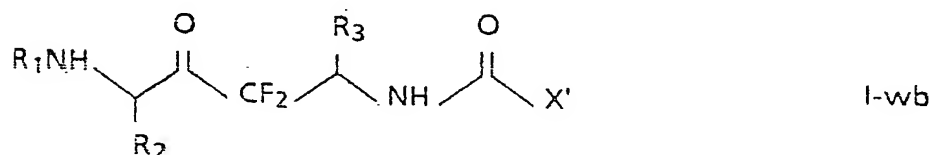
- 5 H-(D)-Pro-Phe-Arg-[CF₂-Gly-NH]COCH₃,
H-(D)-Pro-Phe-Arg-[CF₂-Gly-NH]COOMe,
H-(D)-Pro-Phe-Arg-[CF₂-Gly-NH]*m*-Gly-NH₂,
H-(D)-Pro-Phe-J-1-[CF₂-Gly-NH]COCH₃.

- The compounds of formula (iv) are inhibitors of the kallikreins, tissue or plasma, and therefore inhibit
10 kinin formations. Kinins, generally known to induce pain and vascular permeability associated with inflammation and infection, e.g., bacterial and viral, the inhibition of the kinin formation renders these compounds useful in the alleviation of pain and inflammation. Furthermore, these compounds are useful as male contraceptives in that they will dramatically interfere with normal sperm function. In their end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg
15 to 10 mg/kg per day being preferred.

Another aspect of this invention relates to retroamides of modified Formula I which are useful as inhibitors of the retroviral proteases required for replication, particularly the HIV-1 and HIV-2 viral proteases, the viruses putatively responsible for causing acquired immuno deficiency syndrome (AIDS). These retroamides are of the formula



and



- the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein: R₁, R₂, R₃, n, R₃, R₄, X, Q
40 and Y and Tables I and II are as defined in Formula I with modifications of Groups C', E', F', and X' and R₄ being added as follows:

Group C' contains Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives,

Group E' contains Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives,

- 45 Group F' contains Phe, Tyr, O-methyl tyrosine, Trp, Nal-(l) and their N-methyl derivatives,

Group G' contains Gly,

X' is H or R₇,

R₄ is H, C₁₋₆ alkyl and aralkyl.

- The compounds of Formula I-wa and I-wb which are of particular use as retroviral protease inhibitors
50 are those wherein:

R₁ is P₂, P₃, P₄ with

P₂ is selected from Groups C', E', F', and G', (preferably Asn, Gln and Ala),

P₃ is selected from Groups C', E', F', and G', (preferably Asn, Gln and Ala),

- 55 P₄ is selected from Group C' or β-Ala or β-Val, (preferably Ser or Thr), which may optionally bear an amino protecting group selected from Group K,

R₂ is a residue of the P₁-position α-amino acid of Groups F', E', CHM with Tyr, Phe and CHM being preferred,

R₃ is Gly or Group E', preferably Gly (R₃ not having a nitrogen atom is devoid of N-methyl derivatives),

R_1 is H, C₁₋₆ alkyl, aralkyl, preferably H, C₁₋₆ or benzyl,
 R_2 is a residue of the P₂-position α -amino acid of Group E' or Val,
 X is H or R₇, preferably H or C₁₋₆ alkyl or CHM.

The preferred compounds of Formulae I-wa and I-wb are:

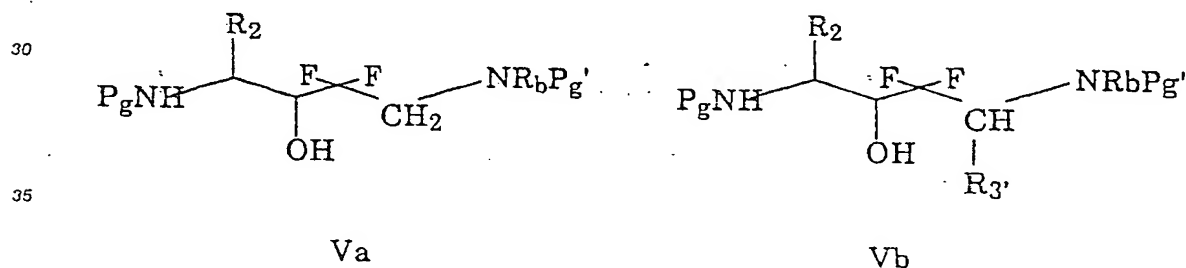
- 5 Ser-Gln-Asn-Tyr[CF₂GlyNH]_m-LeuNH₂,
 Thr-Gln-Asn-Tyr[CF₂GlyNH]_m-LeuNHCHM,
 Ser-Gln-Asn-Tyr[CF₂GlyNH]C(O)H,
 Ser-Gln-Asn-Tyr[CF₂GlyNH]C(O)CHM,
 β -Ala-(O-Me)-Tyr-n-Val-"CHM"-[CF₂GlyNH]Iva
 10 Boc-Phe-n-Val-"CHM"-[CF₂GlyNH]Iva
 Iva-Ser-Gln-Asn-Tyr-[CF₂IleNH]Iva
 Iva-Ser-Phe-n-Val-"CHM"-[CF₂GlyNH]Iva
 Iva-Ser-Gln-Asn-Phe-[CF₂GlyNH]_mValNH₂
 Iva-Ser-Gln-Asn-Tyr-[CF₂IleNH]_mValNH₂

- 15 In their end-use application in the treatment of retroviral infections, the compounds of Formula I-wa and I-wb will be administered at about 1 to 100 mg per kilogram of body weight per day, preferably administered interperitoneally, intravenously and/or orally.

- From the above, it is obvious that in all of the foregoing instances of (Ia) through (Iw), the definitions of R_1 , R_2 , R_3 , X, n and Q are as defined in the generic formula I with the specific preferred embodiments
 20 being further illustrated for each group of enzyme inhibitors. Of course, it is also understood that in those instances wherein the carbonyl moiety of P₁ is in its reduced form, then such compounds are not hydrates.

Having defined the scope of the compounds within the generic invention and within the individual subgeneric groups for each of the individual enzymes, the manner in which such may be prepared will be described and illustrated.

- 25 In general, the compounds of formula I may be prepared using standard chemical reactions analogously known in the art. The key intermediates required for the application of standard peptide coupling techniques may be represented by the formula Va or Vb



40 wherein

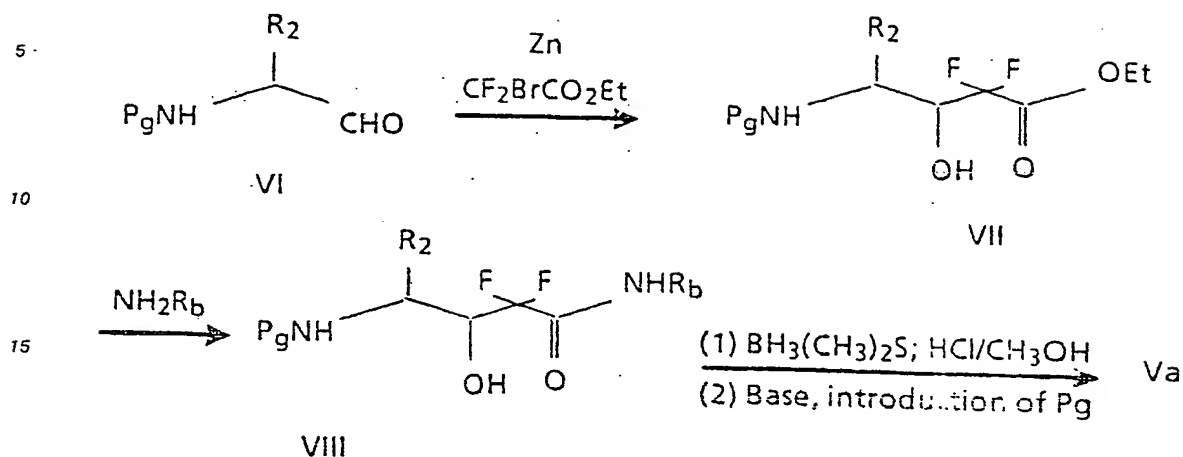
- R_3' is as defined for R_3 and may be a protected form of the residue of the specific α -amino acid involved,
 R_2 is as previously defined, and
 P_g and P_g' are each protecting groups, preferably different from each other so as to facilitate selective
 45 removal depending upon the site, nature and sequence of the reactions required to prepare the final compounds from these intermediates; the selection being according to principles well known and understood by those in the art.

In those instances wherein R_3' represents hydrogen the preparation of the required intermediates (Va) is illustrated by Reaction Scheme A. In those instances wherein R_3' is other than hydrogen then the required intermediates (Vb) are prepared by the methods depicted in Reaction Scheme B.

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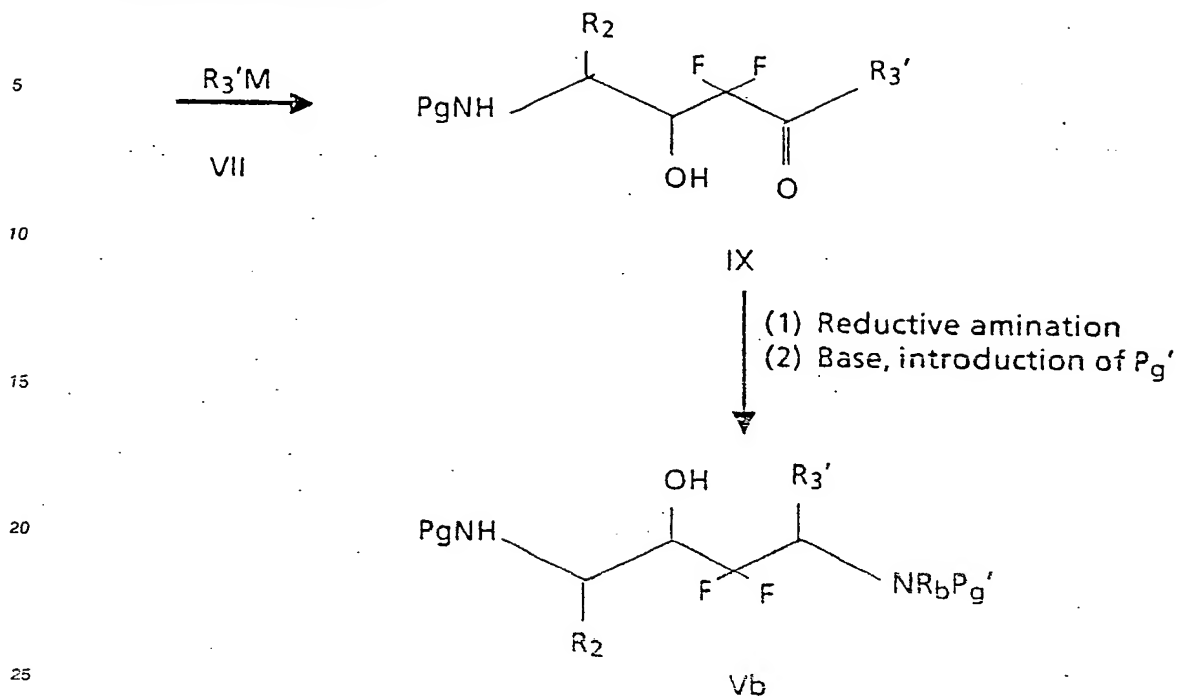
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Reaction Scheme A



In effecting the steps of Reaction Scheme A it is preferred to start with the aldehyde of formula VI wherein the protecting group is a carbamate preferably wherein P_g is benzyloxycarbonyl (CBZ). This so-protected aldehyde is subjected to a condensation reaction with an ester of bromodifluoroacetic acid, preferably the ethyl ester in the presence of zinc. Preferably the reaction is conducted in an anhydrous aprotic solvent, e.g., tetrahydrofuran, ether, dimethoxyethane and the like under a nitrogen atmosphere. The reaction mixture is gently heated under reflux conditions, preferably to about 60°C for about 1-12 hours. The ester (VII) is converted to its primary amide (VIII) by treatment with liquid ammonia under anhydrous conditions, preferably using such solvents as anhydrous diethyl ether. The amidation is initiated at -78°C and following saturation with ammonia the reaction mixture is slowly allowed to rise to room temperature. The so-formed amide is chemically reduced to form the free amine. This chemical reduction is easily effected by reacting the amide with a diborane, preferably as a diborane/dimethylsulfide complex, under a nitrogen atmosphere in an anhydrous aprotic solvent (e.g., THF) under reflux conditions. The reduction yields the desired amine, in the form of an acid (e.g., HCl) salt which by pH adjustment yields the free amine which may be suitably protected with an N-protecting group, e.g., P_g is t-butoxy carbonyl using the standard reaction conditions (e.g., $(\text{BOC})_2\text{O}$, tetrahydrofuran at room temperature) for protecting the amine. Alternatively the free amine may be subjected to reaction conditions designed to build the desired α -amino or peptide moiety on the P' side of the difluoromethylene moiety.

In those instances where R_3 is other than hydrogen then the procedure of Reaction Scheme A is modified to prepare the desired intermediates according to Reaction Scheme B.

Reaction Scheme B

wherein $R_3'M$ is an organometallic reagent, preferably lithium or magnesium coupled to the R_3' moiety (other than hydrogen) desired.

30 The conversion of the ester (VII) to the corresponding R_3' bearing ketone with the organometallic reactant is effected by contacting the reactants together under anhydrous conditions at temperatures of about 0° - 80° C in an aprotic solvent (e.g., tetrahydrofuran). Upon reaction the temperature is slowly allowed to rise to room temperature and the complex is hydrolysed to yield the desired intermediate ketones (IX) which compounds are subjected to reductive amination procedures well known in the art, such as, for

35 example, the procedure described by Borch (see R.F. Borch, et al., *J. Am. Chem. Soc.*, 93, 2897 (1971)). This reductive amination can take place in one or two steps (with isolation of the intermediate imine or enamine). For example, reacting the ketones (IX) with ammonium acetate under slightly acidic conditions in methanol produces the enamine which, when reacted with sodium cyanoborohydride, produces the desired product. Alternatively, the ketones may be treated directly with sodium cyanoborohydride to produce the

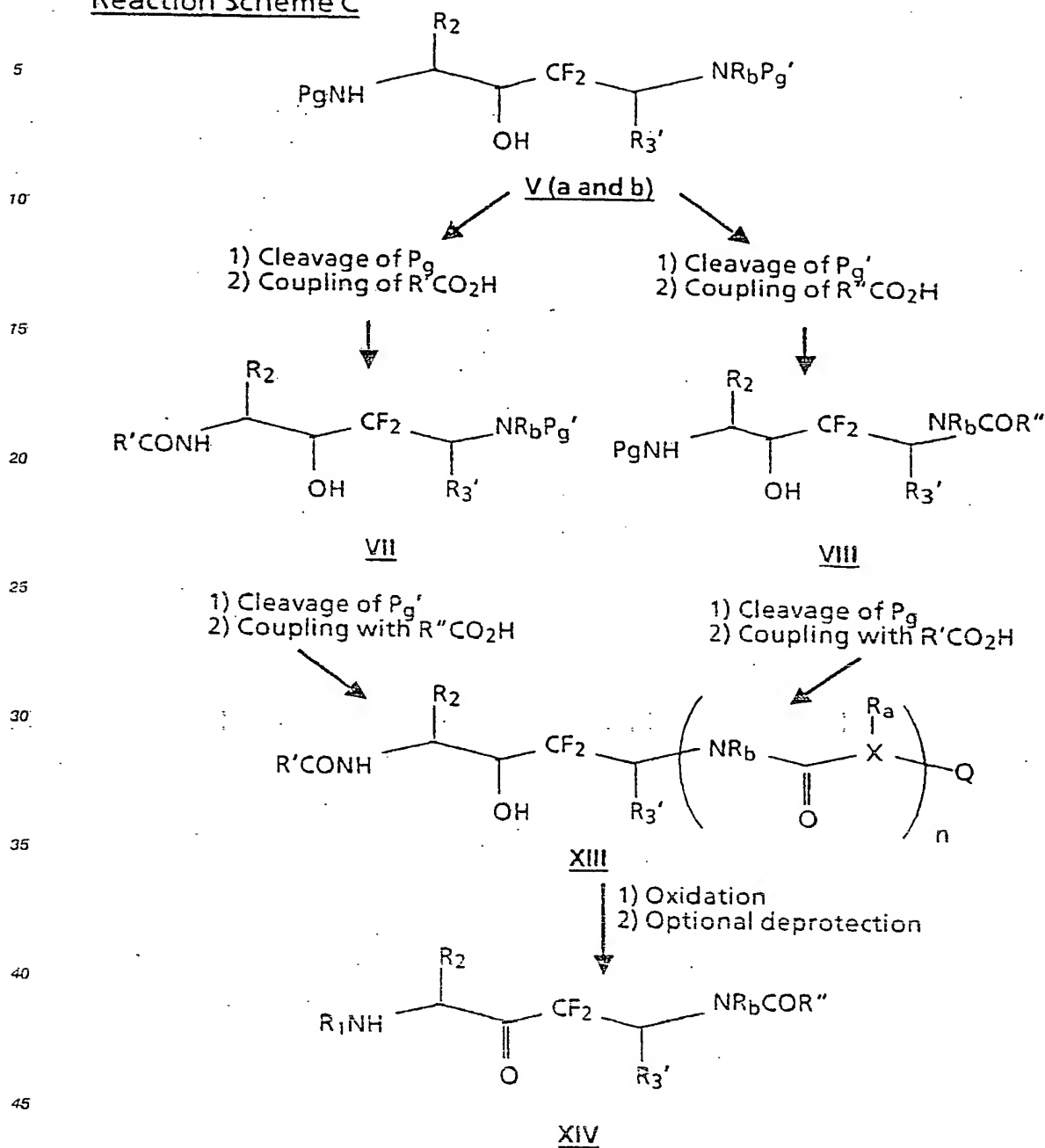
40 desired product. Alternatively, the ketones may be treated directly with sodium cyanoborohydride in the presence of ammonium acetate to produce the desired amines (as its HCl salts) which, in either case, may be neutralized and then the NH_2 moiety may be protected with an appropriate protecting group.

Having obtained the key intermediates of formula V (a and b) standard α -amino acid or peptide coupling procedures may be conducted to prepare the individual compounds of formula I. In practice it is more

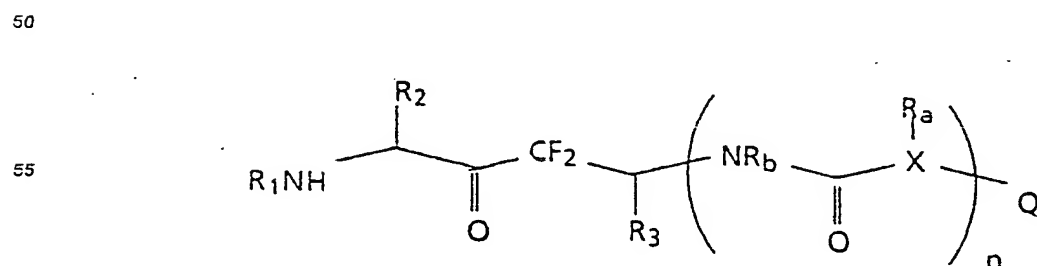
45 convenient to effect coupling on the P' side of the difluoromethylene moiety before coupling the P_2 - P_n moieties because the CBZ protecting group is generally more stable and this facilitates a less difficult route of synthesis for the desired compounds. In general, this series of reactions may be depicted by Reaction Scheme C.

50

55

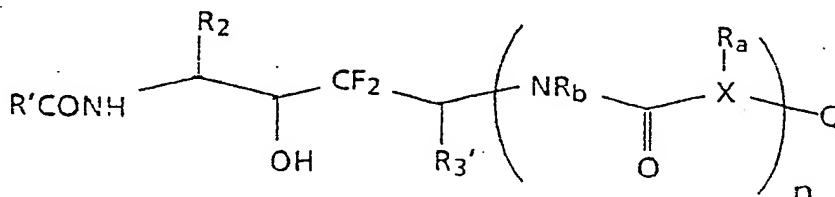
Reaction Scheme C

Formula XIII may otherwise be written as



wherein P_9 , R_2 , R_3 , R_b , P_9' , R_1 are as previously defined and $R'CO_2H$ (leading to VII) is the equivalent of R_1OH of formula I, and $R''CO_2H$ is the equivalent of $(NR_bCOXR_a)_nQ$ of formula I, for example, n is one and $R''CO$ is $COXR_aQ$. The oxidation may be effected via the well-known Swern oxidation procedure, or with a modified Jones reaction using pyridinium dichromate, or a chromic anhydride-pyridinium complex, or with 1,1,1-triacetoxy-2,1-benzoxiodol. Of course, if there are any protecting groups on the residues of the α -amino acid building blocks, such protecting groups may be removed after oxidation. The coupling procedures are effected according to standard procedures well known in the art.

In general the Swern oxidation is effected by reacting about 2 to 10 equivalents of dimethylsulfoxide (DMSO) with about 1 to 6 equivalents of trifluoromethylacetic anhydride $[(CF_3CO)_2O]$ or oxalyl chloride $[(COC)_2]$, said reactants being dissolved in an inert solvent, e.g., methylene chloride (CH_2Cl_2), said reactor being under an inert atmosphere (e.g., nitrogen or equivalently functioning gas) under anhydrous conditions at temperatures of about $-80^\circ C$ to $-50^\circ C$ to form an *in situ* sulfonium adduct to which is added about 1 equivalent of the appropriate alcohols, i.e., from compounds VII and VIII by the coupling with $R'CO_2H$ and $R''CO_2H$, respectively, having the formula



XIII

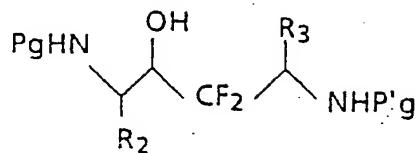
Preferably, the alcohols are dissolved in an inert solvent, e.g., CH_2Cl_2 or minimum amounts of DMSO, and the reaction mixture is allowed to warm to about $-50^\circ C$ (for about 10-20 minutes) and then the reaction is completed by adding about 3 to 10 equivalents of a tertiary amine, e.g., triethylamine, N-methyl morpholine, etc.

In general, the modified Jones oxidation procedure may conveniently be effected by reacting the alcohols (XII) with pyridinium dichromate by contacting the reactants together in a water-trapping molecular sieve powder, e.g., a grounded 3 Angström molecular sieve), wherein said contact is in the presence of glacial acetic acid at about $0^\circ C$ to $50^\circ C$, preferably at room temperature followed by isolation and then optionally removing amine protecting groups.

Alternatively, 1 to 5 equivalents of a chromic anhydride-pyridine complex (i.e., a Sarett reagent prepared *in situ* (see Fieser and Fieser "Reagents for Organic Synthesis" Vol. 1, pp. 145 and Sarett, et al., J.A.C.S. 25, 422, (1953)) said complex being prepared *in situ* in an inert solvent (e.g., CH_2Cl_2) in an inert atmosphere under anhydrous conditions at $0^\circ C$ to $50^\circ C$ to which complex is added 1 equivalent of the alcohols (XII) allowing the reactants to interact for about 1 to 15 hours, followed by isolation and optionally removing amine protecting groups.

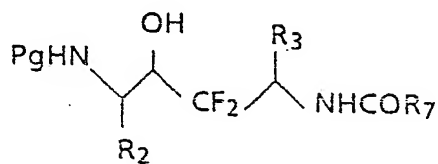
Another alternative process for converting the alcohols (XII) to the desired ketones (XIII) is an oxidation reaction which employs periodane (i.e., 1,1,1-triacetoxy-2,1-benzoxiodol, (see Dess Martin, J. Org. Chem., 48, 4155, (1983))). This oxidation is effected by contacting about 1 equivalent of the alcohols (XII) with 1 to 5 equivalents of periodane (preferably 1.5 equivalents), said reagent being in suspension in an inert solvent (e.g., methylene chloride) under an inert atmosphere (preferably nitrogen) under anhydrous conditions at $0^\circ C$ to $50^\circ C$ (preferably room temperature) and allowing the reactants to interact for about 1 to 48 hours. Optional deprotection of the amine protecting groups may be effected as desired after the ketones have been isolated.

The preparation of the compounds of Formulae I-wa and I-wb follows the same general chemical pathways as outlined and described in Reaction Schemes A and B for the preparation of the key intermediates Va and Vb and also, with minor modifications, essentially follows the reaction pathways of Reaction Scheme C for those compounds wherein solid-phase chemistry is not required (i.e., for those compounds of Formula I-wb) and for those compounds which require solid-phase chemistry for the attachment of the R_1 moieties, the required intermediates (XIX) are prepared essentially along the same lines, with slight modifications, as outlined Reaction Scheme C in preparing compounds XII. The preparation of the I-wa and I-wb compounds is more specifically illustrated in Reaction Schemes D and E; Scheme D being for those compounds of I-wb and Scheme E being for those compounds of I-wa.

Reaction Scheme D

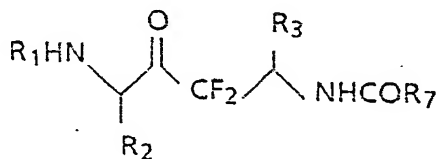
XV

- (1) cleavage of P'g
(2) coupling with $\text{R}_7\text{CO}_2\text{H}$



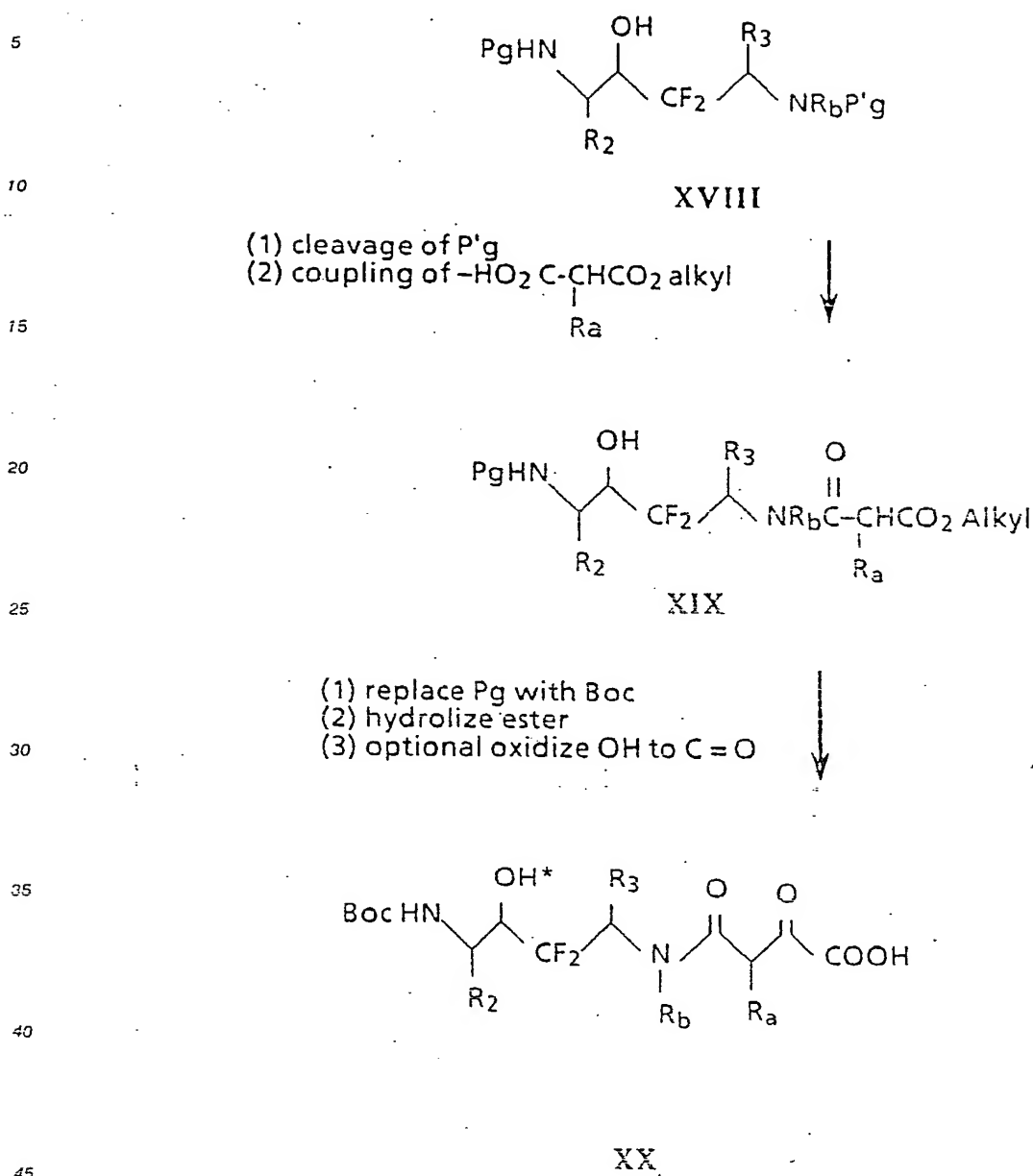
XVI

- (3) remove Pg
(4) couple with $\text{R}'\text{CO}_2\text{H}$
(5) oxidation
(6) deprotection (optional)



XVII

wherein R_1 , R_2 , R_3 and R_7 are as defined for compounds of Formula I-wb. Of course the standard procedures outlined hereinabove for the cleavage of protecting groups, coupling, re-protecting and oxidation are applicable to the foregoing reaction scheme. The moiety $\text{R}'\text{CO}$ of $\text{R}'\text{CO}_2\text{H}$ in the above Reaction Scheme is the equivalent of the R_1 moiety.

Reaction Scheme E

(*or optionally oxidized) and wherein P'g, Pg, R₂, R₃, R_a, R_b are as previously defined above, said cleavage and/or replacing of protecting groups, hydrolysis (e.g., basic conditions) and oxidation procedures being those well-known in the art of peptide chemistry and/or as described above.

50 Following synthesis of the intermediates XX, compounds of Formula I-wa can be subjected to solid-phase sequential and block phase synthesis techniques in order to prepare compounds having the requisite R₁ moiety, and, of course, the hydroxy moiety, if not previously oxidized, may be oxidized by the modified Jones or Dess-Martin techniques described above, said oxidation preferably taking place while the compound is still on the resin.

55 The solid phase sequential procedure can be performed using established automated methods such as by use of an automated peptide synthesizer. In this procedure an amino protected amino acid is bound to a resin support at the carboxy terminal end, the amino acid is deprotected at the amino position at which a peptide linkage is desired, the amino group neutralized with a base and the next amino protected amino

acid in the desired sequence is coupled in a peptide linkage. The deprotection, neutralization and coupling steps are repeated until the desired polypeptide is synthesized. The compounds of the present invention are thus synthesized from their carboxy terminal end to their amino terminal end. The amino protected amino acid can be a conventional amino acid, a derivative or isomer thereof, or a spacer group. The resin support employed can be any suitable resin conventionally employed in the art for the solid phase preparation of polypeptides. The preferred resin is polystyrene which has been cross-linked with from about 0.5 to about 3% divinyl benzene, which has been either benzhydrylamidated, chloromethylated or hydroxymethylated to provide sites for amide or ester formation with the initially introduced amino protected amino acid.

An example of a hydroxymethyl resin is described by Bodansky et al. [Chem. Ind. (London) 38, 1597-98 (1966)]. The preparation of chloromethyl and benzhydrylamine resins are described by Stewart et al. ["Solid Phase Peptide Synthesis", 2nd Edition, Pierce Chemical Co., Rockford, Illinois (1984), Chapter 2, pp. 54-55]. Many of these resins are available commercially. In general, the amino protected amino acid which is desired on the carboxy-terminal end of the peptide is bound to the resin using standard procedures and practices as are well known and appreciated in the art. For example, the amino protected amino acid can be bound to the resin by the procedure of Gisin [Helv. Chem. Acta, 56, 1476 (1973)]. When it is desired to use a resin containing a benzhydrylamine moiety as the resin binding site an amino protected amino acid is coupled to the resin through an amide linkage between its α -carboxylic acid and the amino moiety of the resin. This coupling is effected using standard coupling procedures as described below. Many resin-bound amino acids are available commercially.

The α -amino protecting group employed with each amino acid introduced into the polypeptide sequence may be any such protecting group known in the art. Among the classes of amino protecting groups contemplated are: (1) acyl type protecting groups such as formyl, trifluoroacetyl, phthalyl, p-toluenesulfonyl (tosyl), benzenesulfonyl, nitrophenylsulfonyl, tritylsulfonyl, o-nitrophenoxycarbonyl, and α -chlorobutyryl; (2) aromatic urethane type protecting groups such as benzyloxycarbonyl and substituted benzyloxycarbonyls such as p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α -, α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, and benzhydryloxycarbonyl; (3) aliphatic urethane protecting groups such as tert-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, and allyloxycarbonyl; (4) cycloalkyl urethane type protecting groups such as cyclopentylloxycarbonyl, adamantylloxycarbonyl, and cyclohexylloxycarbonyl; (5) thio urethane type protecting groups such as phenylthiocarbonyl; (6) alkyl type protecting groups such as triphenylmethyl (trityl) and benzyl (Bzl); (7) trialkylsilane protecting groups such as trimethylsilane. The preferred α -amino protecting group is tert-butyloxycarbonyl (Boc). The use of Boc as an α -amino protecting group for amino acids is described by Bodansky et al. in "The Practice of Peptide Synthesis", Springer-Verlag, Berlin (1984), p. 20.

Following the coupling of the amino protected amino acid to the resin support, the α -amino protecting group is removed using any suitable procedure such as by using trifluoroacetic acid, trifluoroacetic acid in dichloromethane, or HCl in dioxane. The deprotection is carried out at a temperature of between 0°C and room temperature. Other standard cleaving reagents may be used for removal of specific amino protecting groups under conditions well known and appreciated in the art.

After removal and neutralization of the α -amino protecting group the next desired amino-protected amino acid is coupled through a peptide linkage. This deprotection, neutralization and coupling procedure is repeated until a polypeptide of the desired sequence is obtained. Alternatively, multiple amino acid groups may be coupled by the solution method prior to coupling with the resin supported amino acid sequence.

The selection and use of an appropriate coupling reagent is within the skill of the ordinary practitioner in the art. Particularly suitable coupling reagents where the amino acid to be added is Gln, Asn, or Arg are N,N-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. The use of these reagents prevents nitrile and lactam formation. Other coupling agents are (1) carbodiimides (e.g., N,N-dicyclohexylcarbodiimide and N-ethyl-N'-(γ -dimethylaminopropyl)carbodiimide); (2) ketenimines; (3) isoxazolium salts (e.g., N-ethyl-5-phenylisoxazolium-3-sulfonate); (4) monocyclic nitrogen containing heterocyclic amides of aromatic character containing one through four nitrogens in the ring such as imidazolidines, pyrazolidines, and 1,2,4-triazolides (specific heterocyclic amides that are useful include N,N-carbonyldiimidazole and N,N-carbonyldi-1,2,4-triazole); (5) alkoxylated acetylene (e.g., ethoxyacetylene); (6) reagents which form a mixed anhydride with the carboxyl moiety of the amino acid (e.g., ethylchloroformate and isobutylchloroformate) or the symmetrical anhydride of the amino acid to be coupled (e.g., Boc-Ala-o-Ala-Boc); (7) nitrogen containing heterocyclic compounds having a hydroxy group on one ring nitrogen (e.g., N-hydroxyphthalimide, N-hydroxysuccinimide, and 1-hydroxybenzotriazole). Other activating reagents and their use in peptide coupling are described by Kapoor [J. Pharm. Sci., 59, 1-27 (1970)]. The generally preferred coupling

method for the amino acids used in the present invention is the use of the symmetrical anhydride as the coupling agent.

The preferred coupling method for Gln, Asn and Arg is to react the protected amino acid, or derivatives or isomers thereof, with N,N-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole (1:1) in N,N-dimethylformamide (DMF) in the presence of the resin or resin-bound amino acid or peptide. The preferred coupling method for other amino acids involves reacting the protected amino acid, or derivative or isomer thereof, with N,N-dicyclohexylcarbodiimide in dichloromethane to form the symmetrical anhydride. The symmetrical anhydride is then introduced into the solid phase reactor containing the resin or resin-bound amino acid or peptide, and the coupling is carried out in a medium of (DMF), or dichloromethane, or DMF: dichloromethane (1:1). A medium of DMF is preferred. The success of the coupling reaction at each stage of the synthesis is monitored by a ninhydrin test as described by Kaiser et al. [Analyt. Biochem. 34,595 (1970)]. In cases where incomplete coupling occurs, the coupling procedure is repeated. If the coupling is still incomplete, the deprotected amine is capped with a suitable capping reagent to prevent its continued synthesis. Suitable capping reagents and the use thereof are well known and appreciated in the art. Examples of suitable capping reagents are acetic anhydride and acetylimidazole as described by Stewart et al. ["Solid Phase Peptide Synthesis", 2nd Ed., Pierce Chemical Co., Rockford, Ill. (1984), Chapter 2, p. 73].

After the desired amino acid sequence has been obtained, the peptide is cleaved from the resin. This can be effected by procedures which are well known and appreciated in the art, such as by hydrolysis of the ester or amide linkage to the resin. It is preferred to cleave the peptide from the benzhydrylamine resin with a solution of dimethyl sulfide, p-cresol, thiocresol, or anisole in anhydrous hydrogen fluoride. The cleavage reaction is preferably carried out at temperatures between about 0° C and about room temperature, and is allowed to continue preferably from between about 5 minutes to about 5 hours.

As is known in the art of solid phase peptide synthesis, many of the amino acids bear side chain functionalities requiring protection during the preparation of the peptide. The selection and use of an appropriate protecting group for these side chain functionalities is within the ability of those skilled in the art and will depend upon the amino acid to be protected and the presence of other protected amino acid residues in the peptide. The selection of such a side chain protecting group is critical in that it must not be removed during the deprotection and coupling steps of the synthesis. For example, when Boc is used as the α -amino protecting group, the following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chains of amino acids such as Lys and Arg; p-methylbenzyl, acetamidomethyl, benzyl (Bzl), or t-butylsulfonyl moieties can be used to protect the sulfide containing side chains of amino acids such as cysteine, homocysteine, penicillamine and the like or derivatives thereof; benzyl (Bzl) or cyclohexyl ester moieties can be used to protect carboxylic acid side chains of amino acids such as Asp, Glu; a benzyl (Bzl) ether can be used to protect the hydroxy containing side chains of amino acids such as Ser and Thr; and a 2-bromocarbobenzoxy (2Br-Z) moiety can be used to protect the hydroxy containing side chains of amino acids such as Tyr. These side chain protecting groups are added and removed according to standard practices and procedures well known in the art. It is preferred to deprotect these side chain protecting groups with a solution of anisole in anhydrous hydrogen fluoride (1:10). Typically, deprotection of side chain protecting groups is performed after the peptide chain synthesis is complete but these groups can alternatively be removed at any other appropriate time. It is preferred to deprotect these side chains at the same time as the peptide is cleaved from the resin.

The compounds are then isolated and purified by standard techniques. The desired amino acids, derivatives and isomers thereof can be obtained commercially or can be synthesized according to standard practices and procedures well known in the art.

The following specific examples are given to illustrate the preparation of this invention although the scope of compounds is meant to be limiting to the scope of compounds embraced by formula I.

EXAMPLE 1

4-Benzylloxycarbonylamino-2,2-difluor-3-hydroxy-6-methylheptanoic acid, ethyl ester

A mixture of 2.080 g (8.3 mmol) of L-N-benzylloxycarbonyl Leucinal and 2.230 g (11 mol) of ethyl bromodifluoroacetate in dry THF (15 ml) was added dropwise to a refluxing suspension of 0.710 g of activated zinc wool in dry tetrahydrofuran (10 ml), under nitrogen. The addition rate was adjusted to maintain gentle reflux of the mixture. After the addition was complete, the solution was stirred for 3 hours at

room temperature. The mixture was quenched by addition of 20 ml ethyl acetate, brine and 1M KHSO₄ (20 ml). The aqueous layer was dried over anhydrous MgSO₄, evaporated and purified by flash chromatography (silica gel, ethyl acetate/cyclohexane, 1:9). 1.130 g of the expected ester were isolated (yield: 36%) (colorless oil).

5 Rf: 0.57 (ethyl acetate/cyclohexane, 1:1).

EXAMPLE 2

10

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-6-methylheptanamide

A stream of dry ammonia was bubbled at -78 °C, through a solution of 0.820 g (2.2 mmol) of 4-benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-6-methylheptanoic acid, ethyl ester in anhydrous diethyl ether (10 ml). After saturation, the temperature was allowed to rise to room temperature with stirring. The excess ammonia was removed, and the solvent evaporated *in vacuo*. The residue was taken off in pentane to yield the expected amide in quantitative yield as a solid.

MS(Cl/NH₃): 345 (MH⁺).

20

EXAMPLE 3

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N⁴-Benzyloxycarbonyl-N¹-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

A solution of 1M BH₃/(CH₃)₂S (1 ml) in dichloromethane was added, under nitrogen, to a mixture of 0.185 g (0.53 mmol) of 4-benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-6-methylheptanamide in anhydrous tetrahydrofuran (10 ml). The mixture was heated at reflux for 3 hours. After cooling to room temperature, methanol (3 ml) and 1N HCl in diethyl ether (6 ml) were added. The solvent was removed in vacuo. The residue was taken off in water and the aqueous layer washed with diethyl ether. The pH of the aqueous phase was adjusted to 10. Diethyl ether extraction afforded the intermediate amine which was directly converted to its N-BOC protected form [(BOC)₂O 1.5 eq; tetrahydrofuran; room temperature]. The expected tert-butylcarbamate was purified by chromatography (silica gel, ethyl acetate/cyclohexane, 1:1). 0.180 g (79% yield).

Rf: 0.63 (ethyl acetate/cyclohexane, (1:1).

40

EXAMPLE 4

N⁴-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine, trifluoroacetate

45

A solution of 0.320 g (0.75 mmol) of N⁴-benzyloxycarbonyl-N¹-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,3-heptanediamine in trifluoroacetic acid (5 ml) was stirred at 0 °C for 30 minutes. The solvent was then removed *in vacuo*, and the residual oil taken off several times in diethyl ether and evaporated to dryness. The expected amine was obtained in quantitative yield and used in the next step without further purification. The pure free amine was isolated through the following procedure: washing the ethereal solution of the trifluoroacetate salt with saturated sodium bicarbonate (three times). The organic phase was dried over anhydrous magnesium sulphate. Filtration and removal of the solvent *in vacuo* left the expected pure N⁴-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine as a white solid. (78% yield).

55

Analysis calculated for $C_{16}H_{24}N_2O_3F_2$						
	C%:	58.17;	H%:	7.32;	N%:	8.48
found	C%:	57.66;	H%:	7.18;	N%:	8.31

5

EXAMPLE 5

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N⁴-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N¹-(2-isovaleryl-amino-propionyl)-6-methyl-1,4-heptanediamine

15

To a stirred solution of 0.130 g (0.75 mmol) of N-isovaleryl-D-alanine in dry acetonitrile (5 ml), under nitrogen, was added 0.075 g (0.75 mmol) of N-methylmorpholine. The resultant solution was cooled to -20 °C. Isobutyl chloroformate (0.103 g; 0.75 mmol) was added dropwise to the cooled reaction mixture. After 10 minutes, a mixture of 0.333 g (0.75 mmol) of N⁴-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine, trifluoroacetate and 0.080 g of N-methylmorpholine in dry dimethylformamide (5 ml) was added to the cooled mixture. After stirring for 4 hours at -20 °C, the temperature of the mixture was allowed to rise to room temperature. Stirring was continued for 15 hours at room temperature. The mixture was then concentrated and placed under high vacuum to remove all the dimethylformamide. The resultant residue was chromatographed (silica gel, ethyl acetate) to give the expected peptide in 65% yield.

20

25

Rf: 0.13 (ethyl acetate/cyclohexane, 1:1).

Analysis calculated for $C_{24}H_{37}N_3O_5F_2$						
	C%:	59.36;	H%:	7.68;	N%:	8.65
found	C%:	59.72;	H%:	7.72;	N%:	8.54.

30

EXAMPLE 6

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2,2-Difluoro-3-hydroxy-N¹-(2-isovalerylaminopropionyl)-6-methyl-1,4-heptanediamine

40

A solution of 0.192 g (0.39 mmol) of N⁴-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N¹-(2-isovalerylaminopropionyl)-6-methyl-1,3-heptanediamine in ethanol (20 ml) was stirred at room temperature, in the presence of 10% Palladium on charcoal (0.010 g) under a hydrogen atmosphere for 5 hours. The hydrogen atmosphere was then replaced by a nitrogen atmosphere and the catalyst was filtered. The solvent was removed *in vacuo* leaving 0.125 g of a white solid (82% yield).

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EXAMPLE 7

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2,2-Difluoro-3-hydroxy-N⁴-(2-isovalerylaminoisovaleryl)-N¹-(2-isovalerylaminopropionyl)-6-methyl-1,3-heptanediamine

55

The title compound was obtained from the amine of Example 6 and N-isovaleryl-L-valine by the procedure described in Example 5.

Rf: 0.45 (methanol/chloroform, 8:92).

MS(Cl/NH₃): 535 (MH⁺).

EXAMPLE 85 2,2-Difluoro-N⁴-(2-isovalerylaminoisovaleryl)-N¹-(2-isovalerylaminopropionyl)-6-methyl-3-oxo-1,4-heptanediamine

A solution of 0.024 g (0.045 mmol) of 2,2-difluoro-3-hydroxy-N⁴-(2-isovalerylaminoisovaleryl)-N¹-(2-isovalerylaminopropionyl)-6-methyl-1,4-heptanediamine in methylene chloride (5 ml) was added to a
 10 suspension of pyridinium dichromate (0.026 g) and 3A molecular sieves (0.038 g), containing 4 liters of glacial acetic acid. Stirring was continued for 15 hours at room temperature. Florisil (0.080 g) was added, stirring continued for 15 minutes and the mixture filtered over sand. Removal of the solvent and chromatography (silica gel, ethyl acetate/acetone, 7:3) afforded the expected difluoroketone as a white solid (0.013 g; 55% yield).

15 Rf: 0.46 (methanol/chloroform 8:92)
 MS(Cl/NH₃): 532 (M⁺).

EXAMPLE 9

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N⁴-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N¹-(2-isopentylaminocarbonylpropionyl)-6-methyl-1,4-heptanediamine

25

To a solution of 0.155 g (0.82 mmol) of 2-isopentylaminocarbonylpropanoic acid, 0.126 g of 1-hydroxybenzotriazole-H₂O and 0.169 g of N,N'-dicyclohexylcarbodiimide in anhydrous methylene chloride (5 ml), at 0 °C was added a mixture of 0.363 g (0.82 mmol) of N⁴-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine, trifluoroacetate and 0.083 g (0.82 mmol) of N-methylmorpholine in methylene
 30 chloride (3 ml). The cooling bath was removed after 1 hour and the reaction was stirred at room temperature overnight. The reaction mixture was then filtered and the filtrate was concentrated in vacuo. The expected peptide was isolated in 83% yield (0.340 g) after column chromatography purification (silica gel, ethyl acetate/chloroform, 1:1).

Rf: 0.16 (ethyl acetate/chloroform, 1:1).

35

Analysis calculated for C ₂₅ H ₃₉ N ₃ O ₅ F ₂						
	C%:	60.10;	H%:	7.87;	N%:	8.41
found	C%:	60.26;	H%:	7.81;	N%:	8.33.

40

EXAMPLE 10

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2,2-Difluoro-3-hydroxy-N¹-(2-isopentylaminocarbonylpropionyl)-6-methyl-1,4-heptanediamine

50

The title compound was prepared from the peptide of Example 9 by the procedure described in Example 6 (96% yield).

55

EXAMPLE 11

2,2-Difluoro-3-hydroxy-N⁴-(2-isovalerylaminoisovaleryl)-N¹-(2-isopentylaminocarbonylpropionyl)-6-methyl-

1,4-heptanediamine

The title compound was prepared from the amine of Example 10 and N-isovaleryl-L-valine by the procedure described in Example 9.

Rf: 0.41 (methanol/chloroform, 8:92)

MS(Cl.NH₃): 549 (MH⁺).

EXAMPLE 122,2-Difluoro-N⁴-(2-isovalerylaminoisovaleryl)-N¹-(2-isopentylaminocarbonylpropionyl)-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared from the alcohol of Example 11 by the procedure described in Example 8 (75% yield).

MS(Cl.NH₃): 547 (MH⁺).

EXAMPLE 134-Benzoyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-phenyl-pentanoic acid, ethyl ester

The title compound was prepared from L-N-benzyloxy-carbonylphenylalaninal and ethyl bromodifluoroacetate by the procedure described in Example 1 (75% yield).

Rf: 0.5 (ethyl acetate/cyclohexane, 1:1).

Analysis calculated for C ₂₁ H ₂₃ NO ₅ F ₂						
	C%:	61.91;	H%:	5.69;	N%:	3.44
found	C%:	62.19;	H%:	5.75;	N%:	3.55

EXAMPLE 144-Benzoyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-phenyl-pentanamide

The title compound was prepared from the ester of Example 13 by the procedure described in Example 2 (98% yield).

EXAMPLE 15N⁴-Benzoyloxycarbonyl-N¹-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared from the amide of Example 14 by the procedure described in Example 3 (64% yield).

EXAMPLE 165 N¹-tert-Butoxycarbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared in quantitative yield from the dicarbamate of Example 15 by the procedure described in Example 6.

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EXAMPLE 1715 N⁶-Benzoyl-N¹-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

A solution of 0.330 g (1.03 mmol) of N¹-tert-butoxy-carbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine and 0.145 g benzoyl chloride (1.03 mmol) in anhydrous tetrahydrofuran was stirred at room temperature for 14 hours in the presence of 0.101 g triethylamine (1 mmol). The solvent was removed *in vacuo*. The residue was taken off in a mixture of methylene chloride and water. The organic phase was dried over MgSO₄. Evaporation and recrystallization from ethyl acetate/pentane afforded the expected compound as a white solid.

25

Analysis calculated for C ₂₃ H ₂₈ N ₂ O ₄ F ₂						
	C%:	63.58;	H%:	6.49;	N%:	6.45
found	C%:	63.68;	H%:	5.75;	N%:	6.85

30

EXAMPLE 18

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N⁶-Benzoyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine, trifluoroacetate

40

The title compound was prepared in quantitative yield from the product of Example 17 by the procedure of Example 4.

EXAMPLE 19

45

N¹-Acetyl-N⁴-benzoyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

50

The title compound was prepared from the amine of Example 18 and acetic anhydride by the procedure described in Example 17 in the presence of 2 equivalents of N-methyl-morpholine.
MS(Cl/NH₃):377 (MH⁺).

EXAMPLE 20

55

N¹-Acetyl-N⁴-benzoyl-2,2-difluoro-3-oxo-5-phenyl-1,4-pentanediamine

The title compound was prepared from the alcohol of Example 19 by the procedure described in Example 8.

Rf: 0.25 (methanol/chloroform, 8:92).

MS(Cl/NH₃):375 (MH⁺).

5

EXAMPLE 21

10

4-Benzoyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-methyl-hexanoic acid, ethyl ester

The title compound was prepared from L-N-benzoyloxycarbonylvalinal and ethyl bromodifluoroacetate by the procedure described in Example 1. (40% yield)

15

EXAMPLE 22

20

4-Benzoyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-methyl-hexanamide

The title compound was prepared in quantitative yield from the ester of Example 21 by the procedure described in Example 2.

25

EXAMPLE 23

30

N⁴-Benzoyloxycarbonyl-N¹-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-5-methyl-1,4-hexanediamine

The title compound was prepared from the amide of Example 22 by the procedure described in Example 3 (yield: 40%).

Rf: 0.50 (ethyl acetate/cyclohexane, 1:1).

35

EXAMPLE 24

40

N¹-tert-Butoxycarbonyl-2,2-difluoro-3-hydroxy-5-methyl-1,4-hexanediamine

The title compound was prepared in quantitative yield from the dicarbamate of Example 23 by the procedure described in Example 6.

45

EXAMPLE 25

50

N¹-tert-Butoxycarbonyl-2,2-difluoro-3-hydroxy-N⁴-(methoxy-succinyl-L-alanyl-L-alanyl-L-prolyl)-5-methyl-1,4-hexane-diamine

55

The title compound was prepared from the amide of Example 24 and methoxy succinyl-L-alanyl-L-alanyl-L-pro-line by the procedure described in Example 5 (yield: 48%).

EXAMPLE 26

5 2,2-Difluoro-3-hydroxy-N⁴-[methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl]-5-methyl-1,4-hexanediamine, trifluoro-
acetate

The title compound was prepared in quantitative yield from the product of Example 25 by the procedure described in Example 4.

EXAMPLE 27

15 2,2-Difluoro-3-hydroxy-N⁴-[methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl]-5-methyl-N¹-(2-methylmalonamoyl)-
1,4-hexanediamine

The title compound was prepared from the amine salt of Example 26 and 2-methylmalonic acid by the procedure described in Example 9.

EXAMPLE 28

25 2,2-Difluoro-N⁴-[methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl]-5-methyl-N¹-(2-methylmalonamoyl)-3-oxo-1,4-
hexanediamine

30 The title compound was prepared from the alcohol of Example 27 by the procedure described in Example 8.

EXAMPLE 29

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5-Benzyloxycarbonylamino-3,3-difluoro-4-hydroxy-7-methyl-2-octanone

40 A 1.6 M solution of methyllithium in 1 ml of diethyl ether was added at -78 °C to a solution of 0.195 g 4-benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-6-methylheptanoic acid, ethyl ester (0.5 mmol) in 5 ml dry tetrahydrofuran. After stirring for 1 hour at -78 °C, the temperature was allowed to rise to room temperature. Stirring was continued for 3 hours at room temperature. The mixture was hydrolyzed and extracted with diethyl ether. The organic layer was washed with brine and dried over MgSO₄. Filtration and removal of the solvent, in vacuo, left an oil, purified by column chromatography (silica gel, ethyl acetate/cyclohexane, 2:8).
 45 0.080 g of the expected ketone was thus isolated as a colorless oil (yield 47%).
 R_f: 0.56 (ethyl acetate/cyclohexane, 1:1).

50

EXAMPLE 30

55 N5-Benzyloxycarbonyl-N2-tert-butoxycarbonyl-3,3-difluoro-4-hydroxy-7-methyl-2,5-octanediamine

A mixture of 0.080 g 5-benzyloxycarbonylamino-3,3-difluoro-4-hydroxy-7-methyl-2-octanone (0.23 mmol), 0.177 g ammonium acetate (2.3 mmol), and 0.010 g sodium cyanoborohydride (0.16 mmol) in 3 ml methanol was stirred at room temperature, under nitrogen, for 20 hours. The mixture was acidified by

addition of 1N HCl (2 ml) and the solvent removed *in vacuo*. The residue was taken off in water, the aqueous phase was washed with diethyl ether. The pH of the aqueous phase was adjusted to 10. Diethyl ether afforded the intermediate amine which was directly converted to its N-BOC protected form. [(BOC)₂O, 1.5 equivalent; tetrahydrofuran; room temperature]. The expected dicarbamate was purified by chromatography (silica gel, ethyl acetate/cyclohexane, 1:1).

EXAMPLE 31

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-(benzyl-oxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from the amine of Example 4 and 2-benzylaminocarbonyl-3-methylbutanoic acid by the procedure described in Example 9 (yield: 55%)
Rf: 0.60 (ethyl acetate)
MS(Cl/NH₃): 548 (MH⁺).

Analysis calculated for C ₂₉ H ₃₉ N ₃ O ₅ F ₂						
	C%:	63.60;	H%:	7.18;	N%:	7.67
found	C%:	63.71;	H%:	7.10;	N%:	7.44.

EXAMPLE 32

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from the compound of Example 31 by the procedure described in Example 6 (yield: 97%).

EXAMPLE 33

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-benzyl-oxycarbonyl-N^{im}-tert-butoxycarbonyl-L-Histidyl]-2,2-di-fluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from N-benzylloxycarbonyl-N^{im}-tert-butoxycarbonyl-L-Histidine and the amine of Example 32 by the procedure described in Example 5 (yield: 64%).
Rf: 0.35 (ethyl acetate).
MS: (Cl/NH₃): 785 (MH⁺).

EXAMPLE 34

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-N^{im}-tert-butoxycarbonyl-L-histidyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from the compound of Example 33 by the procedure described in

Example 6 (yield: 90%).

EXAMPLE 35

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[[N-benzyl-oxycarbonyl-3-(1-naphthyl)alanyl]-Nim-tert-butoxycarbonyl-L-histidyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanedi-amine

The title compound was prepared from N-benzylloxycarbonyl-3-(1-naphthyl)alanine and the amine of Example 34 by the procedure described in Example 5 (yield: 77%).

EXAMPLE 36

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(benzyloxycarbonyl)-L-Phenylalanyl-Nim-tert-butoxycarbonyl-L-histidyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptane-diamine

The title compound was prepared from N-benzylloxycarbonyl-L-phenylalanine and the amine of Example 34 by the procedure described in Example 5 (yield: 60%).

EXAMPLE 37

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from N-(tert-butoxy carbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 32 by the procedure described in Example 5 (yield: 58%).

Rf: 0.56 (methanol/chloroform 8:92).

MS(Cl/NH₃): 760 (MH⁺).

EXAMPLE 38

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 70% yield from the alcohol of Example 37 by the procedure described in Example 8.

Rf: 0.62 (methanol/chloroform 8:92)

MS(Cl/NH₃): 758 (MH⁺).

EXAMPLE 39

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(benzyloxy-carbonyl)-L-phenylalanyl-N^{im}-(tert-butoxycarbonyl)-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 63% yield from the alcohol of Example 36 by the procedure described in Example 8.

Rf: 0.29 (ethyl acetate)

MS(Cl⁻/NH₃): 930(MH⁺).

5

EXAMPLE 40

10

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(benzyloxy-carbonyl)-L-phenylalanyl-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

A mixture of 0.035 g (0.04 mmol) of N¹-(2-benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(benzyloxycarbonyl)-L-phenylalanyl-N¹-(tert-butoxycarbonyl)-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine and trifluoro acetic acid (5 mL) was stirred at 0 °C for one hour. The solvent was removed in vacuo. The residue was taken off in ethyl acetate. The organic solution was washed with 5% sodium bicarbonate and dried over anhydrous magnesium sulphate. Filtration, removal of the solvent in vacuo and purification by flash chromatography (silica gel; chloroform/methanol 98:2 to 92:8) yielded 0.019 g of the title compound as a white solid (61% yield).

MS(DCl/Cl⁻ + /NH₃): 830(MH⁺, 90); 722(83); 683(100); 649(21); 575(70); 504(76).

MS(DCl/Cl⁻ + /NH₃): 830(MH⁺, 90); 722(83); 683(100); 649(21); 575(70); 504(76).

25

EXAMPLE 41

N⁴-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-N¹-(3-methyl-2R-phenylacetylaminobutanoyl)-1,4-heptanediamine

The title compound was prepared in 38% yield from the amine of Example 4 and N-phenylacetyl-D-valine by the procedure described in Example 9.

Rf: 0.52 (silica gel; ethyl acetate)

MS: 565(MNH⁺, 57); 548(MH⁺, 38); 457(85); 440(63); 414(100); 324(11).

EXAMPLE 42

40

2,2-Difluoro-3-hydroxy-6-methyl-N¹-(3-methyl-2R-phenylacetylaminobutanoyl)-1,4-heptanediamine

The title compound was prepared in 63% yield from the carbamate of Example 41 by the procedure described in Example 6.

EXAMPLE 43

50

N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-N¹-(3-methyl-2R-phenylacetylaminobutanoyl)-1,4-heptanediamine

The title compound was prepared in 97% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 42 by the procedure described in Example 9 (solvent used: methylene chloride/dimethylformamide 3:1).

MS(DCl/Cl⁻ + /NH₃): 777(MNH⁺, 66); 760(MH⁺, 100); 703(20); 686(15); 660(15).

EXAMPLE 44

5 N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-N¹-(3-methyl-2R-phenylacetylaminobutanoyl)-3-oxo-1,4-heptanediamine

The title compound was prepared in 50% yield from the alcohol of Example 43 by the procedure described in Example 8.

10 MS: 775(MNH⁺, 30), 758(MH⁺, 100).

EXAMPLE 45

15

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(benzyloxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

20 The title compound was prepared in 77% yield from N-(benzyloxycarbonyl)-L-phenylalanyl-L-n-valyl and the amine of Example 32 by the procedure described in Example 9.

Rf: 0.47 (silica gel; chloroform/methanol 92:8)

MS(DCI/CI + /NH₃): 811(MNH⁺, 25); 794(MH⁺, 9); 703(100); 686(18); 660(5); 613(7).

25

EXAMPLE 46

30 N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(benzyloxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 82% yield from the alcohol of Example 45 by the procedure described in Example 8.

35 Rf: 0.64 (silica gel; chloroform/methanol 92:8)

MS(DCI/CI + /CH₄): 792(MH⁺).

EXAMPLE 47

40

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(benzyloxycarbonyl-N^{1m}-tert-butoxycarbonyl-L-histidyl)]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

45

The title compound was prepared in 60% yield from the alcohol of Example 33 by the procedure described in Example 8.

Rf: 0.44 (silica gel; ethyl acetate)

MS(DCI/CI + /NH₃): 783(MH⁺, 40); 683(66); 575(38); 457(100).

50

EXAMPLE 48

55

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(benzyloxycarbonyl-L-histidyl)-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 54% yield from the ketone of Example 47 by the procedure described in Example 40.

Rf: 0.19 (silica gel; chloroform/methanol 92:8)

MS(DCI/CI + \cdot NH₃): 683(MH⁺, 100); 575(60).

EXAMPLE 49

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[[N-(benzyloxycarbonyl-3-(1-naphthyl)alanyl]-N^{im}-tert-butoxycarbonyl-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 50% yield from the alcohol of Example 35 by the procedure described in Example 8.

Rf: 0.36 (silica gel; ethyl acetate)

MS(DCI/CI + \cdot NH₃): 980(MH⁺, 2); 880(16); 772(100); 753(26); 732(90); 575(23); 498(100).

EXAMPLE 50

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[[N-(benzyloxycarbonyl-3-(1-naphthyl)alanyl]-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared from the carbamate of Example 49 by the procedure described in Example 40.

EXAMPLE 51

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-N^{im}-(tert-butoxycarbonyl)-L-histidyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 50% yield from (N-tert-butoxycarbonyl)-L-phenylalanine and the amine of Example 34 by the procedure described in Example 5.

Rf: 0.43 (silica gel; ethyl acetate).

EXAMPLE 52

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-N^{im}-(tert-butoxycarbonyl)-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 53% yield from the alcohol of Example 51 by the procedure described in Example 8.

Rf: 0.57 (silica gel; ethyl acetate)

MS(DCI/CI + \cdot NH₃): 896.5 (MH⁺, 24); 796.4(76); 696.4(4); 649.4(100).

EXAMPLE 53

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

To a solution of N¹-(2-benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-N³-(tert-butoxycarbonyl)-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine (0.179 g, 0.2 mmol) in methanol (3 mL) was added anhydrous potassium carbonate (0.063 g, 0.46 mmol). The mixture was stirred 1.5 hours at room temperature. Acetic acid (0.2 mL) was added and the mixture was evaporated to dryness, at reduced pressure. The residue was taken off in ethyl acetate. The organic solution was washed with 5% sodium bicarbonate, and dried over anhydrous magnesium sulphate. Filtration, removal of the solvent in vacuo and purification by flash chromatography yielded the title compound as a white solid.

EXAMPLE 54

N¹-(2-Benzylaminocarbonylpropanoyl)-N⁴-(benzyloxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 81% yield from 2-benzylaminocarbonylpropanoic acid and the amine of Example 4 by the procedure described in Example 9.

Rf: 0.48 (silica gel; ethyl acetate)

MS(DCI/Cl + /NH₃): 537((MNH⁺₄, 96); 520(MH⁺, 100); 420(10); 386(28); 242(37); 225(89).

EXAMPLE 55

N¹-(2-Benzylaminocarbonylpropanoyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 87% yield from the carbamate of Example 54 by the procedure described in Example 6.

EXAMPLE 56

N¹-(2-Benzylaminocarbonylpropanoyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 66% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 55 by the procedure described in Example 5.

Rf: 0.40 (silica gel; chloroform/methanol 92:8)

MS(DCI/Cl + /NH₃): 749 (MNH⁺₄, 28); 732(MH⁺, 82); 632(39); 282(96); 265(100).

Analysis calculated for C ₃₈ H ₅₅ N ₅ O ₇ F ₂ :						
Found:	C%:	62.36;	H%:	7.57;	N%:	9.57.
	C%:	62.13;	H%:	7.59;	N%:	9.34.

EXAMPLE 57

N¹-(2-Benzylaminocarbonylpropanoyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 79% yield from the alcohol of Example 56 by the procedure described in Example 8.

Rf: 0.52 (silica gel; chloroform/methanol 92:8)

MS(DCI/Cl + NH₃): 748(MNH⁺₄, 16); 731(MH⁺, 100).

Analysis calculated for: C ₃₈ H ₅₃ N ₅ O ₇ F ₂						
Found	C%:	62.53;	H%:	7.32;	N%:	9.59.
	C%:	62.10;	H%:	7.37;	N%:	9.53.

EXAMPLE 58

N¹-(2-Benzylaminocarbonylacetyl)-N⁴-(benzyloxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 65% yield from 2-benzylaminocarbonylacetic acid and the amine of Example 4 by the procedure described in Example 9.

Rf: 0.32 (silica gel; ethyl acetate)

MS(DCI/Cl + NH₃): 523(MNH⁺₄, 100); 506(MH⁺, 26).

Analysis calculated for C ₂₆ H ₃₃ N ₃ O ₅ F ₂						
Found:	C%:	61.77;	H%:	6.58;	N%:	8.31.
	C%:	61.50;	H%:	6.59;	N%:	8.23.

EXAMPLE 59

N¹-(2-Benzylaminocarbonylacetyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 93% yield from the carbamate of Example 58 by the procedure described in Example 6.

EXAMPLE 60

N¹-(2-Benzylaminocarbonylacetyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 33% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 59 by the procedure described in Example 5.

Rf: 0.42 (silica gel; chloroform/methanol 92/8)

MS(DCI/Cl + NH₃): 736(MNH⁺₄, 58); 719(MH⁺, 100).

EXAMPLE 61

5 N¹-(2-Benzylaminocarbonylacetyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 46% yield from the alcohol of Example 50 by the procedure described in Example 8.

10 m.p.: 81 °C

Rf: 0.34 (silica gel; ethyl acetate)

MS(DCI/Cl⁺/NH₃): 716.5(MH⁺, 100).

EXAMPLE 62

20 N¹-(2-Benzylaminocarbonylpropanoyl)-N⁴-(tert-butoxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

A mixture of 0.157 g of N¹-(2-benzylaminocarbonylpropanoyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine (Example 55) and di-tert-butyl dicarbonate (0.088 g) in anhydrous tetrahydrofuran (5 mL) was stirred at room temperature for 15 hours. Removal of the solvent in vacuo and chromatography (silica
25 gel; ethyl acetate: cyclohexane 3/7) yielded 0.140 g of the title compound (72% yield).

Rf: 0.50 (silica gel; ethyl acetate)

MS(DCI/Cl⁺/NH₃): 503(MNH₄⁺, 60); 486(MH⁺, 100).

EXAMPLE 63

35 N¹-(2-Benzylaminocarbonylpropanoyl)-N⁴-(tert-butoxycarbonyl)-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 63% yield from the alcohol of Example 62 by the procedure described in Example 8.

Rf: 0.60 (silica gel; ethyl acetate)

40 MS(DCI/Cl⁺/NH₃): 501(MNH₄⁺, 100); 484(MH⁺, 45).

EXAMPLE 64

45 N¹-(2-Benzylaminocarbonylpropanoyl)-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine, hydrochloride

A mixture of 0.085 g of ketone of Example 63 and a saturated solution of hydrogen chloride in diethyl ether (6 mL) was stirred at room temperature for 15 hours. A white precipitate formed during that time. The solid was filtered off, rinsed thoroughly with pentane and dried in high vacuo.

Rf: 0.46 (silica gel; AcOH/BuOH/H₂O, 2:6:2)

MS(DCI/Cl⁺/NH₃): 384(MH⁺, 100); 344(74).

EXAMPLE 65

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-(tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 65% yield from the amine of Example 32 by the procedure described in Example 62.

Rf: 0.62 (silica gel; ethyl acetate)

MS(DCI/Cl + /NH₃): 531(MNH⁺₄, 10); 514(MH⁺, 100).

EXAMPLE 66

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-(tert-butoxycarbonyl)-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 79% yield from the alcohol of Example 65 by the procedure described in Example 8.

Rf: 0.75 (silica gel; ethyl acetate)

MS(DCI/Cl + /NH₃): 529(MNH⁺₄, 70); 512(MH⁺, 100); 489(14).

EXAMPLE 67

N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-(tert-butoxycarbonyl)-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine, hydrochloride

the title compound was prepared in 94% yield from the ketone of Example 66 by the procedure described in Example 64.

m.p.: 110 °C (decomposition)

Rf: 0.65 (silica gel; AcOH/BuOH/H₂O, 2:6:2)

MS(DCI/Cl + /NH₃): 412(MH⁺, 75); 372(45); 103 (100)

Analysis calculated for C ₂₁ H ₃₂ N ₃ O ₃ F ₂ Cl, H ₂ O:						
Found:	C%:	54.13;	H%:	7.35;	N%:	9.02.
	C%:	54.55;	H%:	7.37;	N%:	8.76.

EXAMPLE 68

N⁴-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-N¹-(2R-phenylacetylaminopropanoyl)-1,4-heptanediamine

The title compound was prepared in 67% yield from 2R-phenylacetylaminopropanoic acid and the amine of Example 4 by the procedure described in Example 9.

m.p.: 146 °C

MS(DCI/Cl + /NH₃): 537(MNH⁺₄, 100); 520(MH⁺, 42); 386(20); 153(55)

Analysis calculated for C ₂₇ H ₃₅ N ₃ O ₅ F ₂ :						
	C%:	62.41;	H%:	6.79;	N%:	8.09.
Found:	C%:	62.34;	H%:	6.83;	N%:	7.93.

EXAMPLE 692,2-Difluoro-3-hydroxy-6-methyl-N¹-(2R-phenylacetylaminopropanoyl)-1,4-heptanediamine

The title compound was prepared in 95% yield from the carbamate of Example 68 by the procedure described in Example 6.

EXAMPLE 70N⁴-(tert-Butoxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-N¹-(2R-phenylacetylaminopropanoyl)-1,4-heptanediamine

The title compound was prepared in 78% yield from the amine of Example 69 by the procedure described in Example 62.

Rf: 0.50 (silica gel; ethyl acetate)

MS(DCI/Cl⁺/NH₃): 503(MNH⁺₄, 93); 486(MH⁺, 100);.

EXAMPLE 71N⁴-(tert-Butoxycarbonyl)-2,2-difluoro-6-methyl-N¹-(2R-phenylacetylaminopropanoyl)-3-oxo-1,4-heptanediamine

The title compound was prepared in 96% yield from the alcohol of Example 70 by the procedure described in Example 8.

Rf: 0.60 (silica gel; ethyl acetate)

MS(DCI/Cl⁺/NH₃): 501(MNH⁺₄, 55); 484(MH⁺, 74); 466(18); 445(44); 428(100).

EXAMPLE 722,2-Difluoro-6-methyl-N¹-(2R-phenylacetylaminopropanoyl)-3-oxo-1,4-heptanediamine, hydrochloride

The title compound was prepared in 91% yield from the ketone of Example 71 by the procedure described in Example 64.

m.p.: 110 °C (decomposition)

Rf: 0.59 (silica gel; AcOH/BuOH/H₂O, 2:6:2)

MS(DCI/Cl⁺/NH₃): 384(MH⁺, 100); 344(34); 153(85); 103(85).

EXAMPLE 73

N⁴-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-N¹-(3-methylbutanoyl)-1,4-heptanediamine

The title compound was prepared in 86% yield from isovaleric acid and the amine of Example 4 by the procedure described in Example 5.

Rf: 0.33 (silica gel; ethyl acetate/cyclohexane 1:1)

MS(DCI/Cl + /NH₃): 432(MNH⁺, 100); 415(MH⁺, 57); 281(70).

EXAMPLE 74

2,2-Difluoro-3-hydroxy-6-methyl-N¹-(3-methylbutanoyl)-1,4-heptanediamine

The title compound was prepared in 89% yield from the carbamate of Example 73 by the procedure described in Example 6.

EXAMPLE 75

N⁴-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-N¹-(3-methylbutanoyl)-1,4-heptanediamine

The title compound was prepared in 82% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 74 by the procedure described in Example 9.

Rf: 0.41 (silica gel; chloroform/methanol 92:8)

MS(DCI/Cl + /NH₃): 644(MNH⁺, 61); 627(MH⁺, 100).

EXAMPLE 76

N⁴-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-N¹-(3-methylbutanoyl)-3-oxo-1,4-heptanediamine

The title compound was prepared in 60% yield from the alcohol of Example 75 by the procedure described in Example 8.

Rf: 0.49 (silica gel; chloroform/methanol 92:8)

MS(DCI/Cl + /NH₃): 643(MNH⁺, 100); 625(MH⁺, 35).

Analysis calculated for: C ₃₂ H ₅₀ N ₄ O ₆ F ₂ :						
Found:	C%:	61.52;	H%:	8.07;	N%:	8.97.
	C%:	61.56;	H%:	8.35;	N%:	8.81.

EXAMPLE 77

N⁴-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The trifluoroacetic acid salt of the title compound was prepared in quantitative yield from the carbamate of Example 15 by the procedure described in Example 4. An ethereal solution of this TFA salt was washed with saturated sodium bicarbonate (3 times) and dried over anhydrous magnesium sulphate. Filtration and removal of the solvent in vacuo yielded the title compound in 88% yield as a white solid.

MS(DCl/Cl + NH₃): 382(MNH⁺₄, 3); 365(MH⁺, 100).

EXAMPLE 78N¹-Acetyl-N⁴-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared in 70% yield from acetic anhydride and the amine of Example 77 by the procedure described in Example 17.

Rf: 0.39 (silica gel; ethyl acetate)

MS(DCl/Cl + NH₃): 424(MNH⁺₄, 100); 407(MH⁺, 23); 273(62).

EXAMPLE 79N¹-Acetyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared in 84% yield from the carbamate of Example 78 by the procedure described in Example 6.

EXAMPLE 80N¹-Acetyl-N⁴-(N-acetyl-L-Leucyl)-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared in 72% yield from N-acetyl-L-leucine and the amine of Example 79 by the procedure described in Example 9.

Rf: 0.17 (silica gel; chloroform/methanol 92:8)

MS(DCl/Cl + NH₃): 445(MNH⁺₄, 100); 428(MH⁺, 54).

Analysis calculated for: C ₂₁ H ₃₁ N ₃ O ₄ F ₂						
	C%:	59.00;	H%:	7.31;	N%:	9.83.
Found:	C%:	58.98;	H%:	7.24;	N%:	9.42.

EXAMPLE 81N¹-Acetyl-N⁴-(N-acetyl-L-Leucyl)-2,2-difluoro-3-oxo-5-phenyl-1,4-pentanediamine

The title compound was prepared in 73% yield from the alcohol of Example 80 by the procedure described in Example 8.

Rf: (silica gel; chloroform/methanol 92:8)

MS(DCI/Cl⁺/NH₃): 443(MNH⁺, 100); 426(MH⁺, 23).

Analysis calculated for C ₂₁ H ₂₉ N ₃ O ₄ F ₂ :						
	C%:	59.28;	H%:	6.87;	N%:	9.88.
Found:	C%:	59.51;	H%:	7.02;	N%:	9.65.

EXAMPLE 82

N⁴-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-methyl-1,4-hexanediamine, trifluoroacetate

The title compound was prepared in 66% yield from the carbamate of Example 23 by the procedure described in Example 77.

EXAMPLE 83

N¹-Acetyl-N⁴-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-methyl-1,4-hexanediamine

The title compound was prepared in 83% yield from the amine of Example 82 and acetic anhydride by the procedure described in Example 17.

EXAMPLE 84

N¹-Acetyl-2,2-difluoro-3-hydroxy-5-methyl-1,4-hexanediamine

The title compound was prepared in 89% yield from the carbamate of Example 83 by the procedure described in Example 6.

EXAMPLE 85

N¹-Acetyl-2,2-difluoro-3-hydroxy-N⁴-(methoxysuccinyl)-L-alanyl-L-alanyl-L-prolyl-5-methyl-1,4-hexanediamine

The title compound was prepared in 43% yield from methoxysuccinyl-L-alanyl-L-alanyl-L-proline and the amine of Example 84 by the procedure described in Example 5.

Rf: 0.19 (silica gel; chloroform/methanol 92:8)

MS(DCI/Cl⁺/NH₃): 596(MH⁺, 23); 563(100); 546(41).

EXAMPLE 86

N¹-Acetyl-2,2-difluoro-N⁴-(methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl)-5-methyl-3-oxo-1,4-hexanediamine

The title compound was prepared in 60% yield from the carbamate of Example 85 by the procedure described in Example 8.

Rf: 0.23 (silica gel; chloroform/methanol 92:8)

MS(DCI/Cl + /NH₃): 593(MNH⁺₄, 100); 576(MH⁺, 52).

Analysis calculated for C ₂₅ H ₃₉ N ₅ O ₈ F ₂ :						
	C%:	52.17;	H%:	6.83;	N%:	12.17.
Found:	C%:	52.54;	H%:	6.95;	N%:	11.58.

EXAMPLE 87N⁴-Benzyloxycarbonyl-N¹-(2-methylpropyloxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 89% yield from isobutylchloroformate and the amine of Example 4 by the procedure described in Example 17.

Rf: 0.45 (silica gel; ethyl acetate/cyclohexane 1:1)

MS(DCI/Cl + /NH₃): 448(MNH⁺₄, 100); 431(MH⁺, 28); 340(15); 297(57).

EXAMPLE 882,2-Difluoro-3-hydroxy-6-methyl-N¹-(2-methylpropyloxycarbonyl)-1,4-heptanediamine

The title compound was prepared in 93% yield from the carbamate of Example 87 by the procedure described in Example 6.

EXAMPLE 89N⁴-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-N¹-(2-methylpropyloxycarbonyl)-1,4-heptanediamine

The title compound was prepared in 62% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 88 by the procedure described in Example 5.

Rf: 0.60 (silica gel; chloroform/methanol 92:8)

MS(DCI/Cl + /NH₃): 660(MNH⁺₄, 30); 643(MH⁺, 100).

EXAMPLE 90N⁴-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-N¹-(2-methylpropyloxycarbonyl)-3-oxo-1,4-heptanediamine

The title compound was prepared in 84% yield from the alcohol of Example 89 by the procedure

described in Example 8.

m.p.: 131 °C

Rf: 0.44 (silica gel; ethyl acetate/cyclohexane 1:1)

MS(DCl/Cl + NH₃): 658(MNH⁺, 100); 641(MH⁺, 98)

Analysis calculated for C ₃₂ H ₅₀ N ₄ O ₇ F ₂ :						
	C%:	59.98;	H%:	7.86;	N%:	8.74.
Found:	C%:	60.40;	H%:	8.11;	N%:	8.39.

EXAMPLE 91

N⁴-Benzoyl-N¹-(2-benzyloxycarbonylacetyl)-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared in 42% yield from 2-benzyloxycarbonylacetic acid and the amine of Example 18 by the procedure described in Example 9.

Rf: 0.17 (silica gel; ethyl acetate/cyclohexane 1:1)

MS(Cl/NH₃): 511(MH⁺, 100).

EXAMPLE 92

N⁴-Benzoyl-N¹-(2-benzyloxycarbonylacetyl)-2,2-difluoro-3-oxo-5-phenyl-1,4-pentanediamine

The title compound was prepared in 50% yield from the alcohol of Example 91 by the procedure described in Example 8.

EXAMPLE 93

N⁴-Benzoyl-N¹-(2-carboxyacetyl)-2,2-difluoro-3-oxo-5-phenyl-1,4-pentanediamine

The title compound was prepared in quantitative yield from the ester of Example 92 by the procedure described in Example 6.

EXAMPLE 94

N-Benzyloxycarbonyl-3-cyclohexylalanine

To a solution of 3-cyclohexylalanine, hydrochloride (4.75 g, 22.8 mmol) in 2N sodium hydroxide (11.4 mL) were added at 0 °C, simultaneously, a solution of benzylchloroformate (3.2 mL, 36 mmol) in tetrahydrofuran (10 mL) and 2N sodium hydroxide (11.4 mL). (The pH of the mixture was maintained around 9-10 by addition of 2N sodium hydroxide.) The mixture was stirred for 1.5 hours. The solution was washed with diethyl ether (3 x 20 mL). The aqueous phase was acidified to pH 2 with 3N aqueous hydrochloric acid and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous magnesium sulphate. Filtration and removal of the solvent in vacuo left 4.80 g of the expected product

(yellow oil, 69% yield).

Rf: 0.75 (silica gel; AcOH/BuOH/H₂O 2:6:2).

EXAMPLE 95

2-Benzoyloxycarbonylamino-3-cyclohexyl-N,O-dimethyl propane-hydroxamate

To a solution of N-benzoyloxycarbonyl-3-cyclohexylalanine (4.60 g, 15 mmol) in anhydrous methylene chloride (60 mL) were added, at 0 °C, dicyclohexylcarbodiimide (3.09 g, 15 mmol) and 1-hydroxybenzotriazolehydrate (2.29 g, 15 mmol). After stirring for 0.25 hours at 0 °C, N,O,-dimethylhydroxylamine hydrochloride (1.46 g, 15 mmol) and N-methylmorpholine (1.51 g, 15 mmol) were added to the mixture. The mixture was stirred for 20 hours while the temperature was allowed to rise to room temperature. The precipitate was filtered off. The solvent was removed in vacuo and the mixture was purified by chromatography (silica gel; ethyl acetate/cyclohexane 2:8) yielding 3.60 g of the expected hydroxamate (69% yield). Rf: 0.38 (silica gel; ethyl acetate/cyclohexane 1:1, UV, I₂).

EXAMPLE 96

N-Benzoyloxycarbonyl-3-cyclohexylalaninal

A mixture of 2-benzoyloxycarbonylamino-3-cyclohexyl-N,O-dimethylpropanehydroxamate (3.58 g, 10.3 mmol), and lithium aluminiumhydride (0.44 g, 11.6 mmol) in anhydrous diethyl ether (100 mL) was stirred at 0 °C for 1 hour. 1M Potassium hydrogenosulphate (25 mL) was added. The mixture was stirred for 0.5 hour and extracted with diethyl ether (2 x 25 mL).

The combined organic layers were washed with 2N HCl (3 x 20 mL), water (1 x 20 mL), a saturated solution of sodium bicarbonate (1 x 20 mL), brine (20 mL) and dried over anhydrous magnesium sulphate. Filtration and removal of the solvent in vacuo left 2.52 g of the expected aldehyde (85%, yellowish oil) used in the next step without further purification.

EXAMPLE 97

4-Benzoyloxycarbonylamino-5-cyclohexyl-2,2-difluoro-3-hydroxypentanoic acid, ethyl ester

The title compound was prepared in 37% yield from N-benzoyloxycarbonyl-3-cyclohexylalaninal, ethyl bromodifluoroacetate and zinc by the procedure described in Example 1.

Rf: 0.57 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 98

4-Benzoyloxycarbonylamino-5-cyclohexyl-2,2-difluoro-3-hydroxypentanamide

The title compound was prepared in 97% yield from the ester of Example 97 by the procedure described in Example 2.

Rf: 0.53 (silica gel; ethyl acetate)

MS(DCI/Cl + /NH₃): 402(MNH₄⁺, 86); 385(MH⁺, 13); 294(23); 169(40); 126(100).

EXAMPLE 99

5 N⁴-Benzyloxycarbonyl-N¹-(tert-butoxycarbonyl)-5-cyclohexyl-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 51% yield from the amide of Example 98 by the procedure described in Example 3.

Rf: 0.59 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 100

15 N⁴-Benzyloxycarbonyl-5-cyclohexyl-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 60% yield from the carbamate of Example 99 by the procedure described in Example 77.

EXAMPLE 101

25 N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-benzyloxycarbonyl-5-cyclohexyl-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 58% yield from 2-benzylaminocarbonyl-3-methylbutanoic acid and the amine of Example 100 by the procedure described in Example 9.

Rf: 0.60 (silica gel; ethyl acetate)

Analysis calculated for C ₃₂ H ₄₃ N ₃ O ₅ F ₂						
	C%:	65.40;	H%:	7.37;	N%:	7.15.
Found:	C%:	65.01;	H%:	7.42;	N%:	7.06.

EXAMPLE 102

45 N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-5-cyclohexyl-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 82% yield from the carbamate of Example 101 by the procedure described in Example 6.

EXAMPLE 103

55 N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-(N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl)-5-cyclohexyl-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 60% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine

and the amine of Example 102 by the procedure described in Example 5.

Rf: 0.46 (silica gel; chloroform/methanol 92:8)

MS(DCl/Cl + /NH₃): 817(MNH₄⁺, 10); 800(MH⁺, 100); 700(60).

5

Analysis calculated for: C ₄₃ H ₆₃ N ₅ O ₇ F ₂						
	C%:	64.56;	H%:	7.94;	N%:	8.75.
Found:	C%:	64.47;	H%:	8.13;	N%:	8.58.

10

EXAMPLE 104

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N¹-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N⁴-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-5-cyclohexyl-2,2-difluoro-3-oxo-1,4-pentanediamine

20

The title compound was prepared in 64% yield from the alcohol of Example 103 by the procedure described in Example 8.

Rf: 0.53 (silica gel; chloroform/methanol 92:8)

MS(DCl/Cl + /NH₃): 815(MNH₄⁺, 10); 798(MH⁺, 100).

25

EXAMPLE 105

30

Ethyl 4-benzyloxycarbonylamino-2,2-difluoro-3-hydroxy butanoate

The title compound was prepared in 33% yield from N-benzyloxycarbonylglycinal, ethyl bromodifluoroacetate and zinc by the procedure described in Example 1.

Rf: 0.45 (silica gel; ethyl acetate/cyclohexane 1:1).

35

EXAMPLE 106

40

4-Benzylloxycarbonylamino-2,2-difluoro-3-hydroxy butanamide

The title compound was prepared in 95% yield from the ester of Example 105 by the procedure described in Example 2.

Rf: 0.49 (silica gel; ethyl acetate/cyclohexane 1:1).

45

EXAMPLE 107

50

N¹-Benzyloxycarbonyl-N¹-(tert-butoxycarbonyl)-2,2-difluoro-3-hydroxy-1,4-butanediamine

The title compound was prepared in 48% yield from the amide of Example 106 by the procedure described in Example 3.

Rf: 0.42 (silica gel; ethyl acetate/cyclohexane 1:1)

MS(DCl/Cl + /NH₃): 392(MNH₄⁺, 59); 375(MH⁺, 20); 258(15); 241(100).

EXAMPLE 1085 Ethyl 4-benzyloxycarbonylamino-2,2-difluoro-3-hydroxy pentanoate

The title compound was prepared in 50% yield from N-benzyloxycarbonylalaninal, ethyl bromodifluoroacetate and zinc by the procedure described in Example 1.
Rf: 0.49 (silica gel; ethyl acetate/cyclohexane 1:1).

10

EXAMPLE 109

15

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy pentanamide

The title compound was prepared in 90% yield from the ester of Example 108 by the procedure described in Example 2.

20

Rf: 0.50 (silica gel; ethyl acetate/cyclohexane 1:1)

MS(DCI/CI + NH_3): 320(MNH^+ , 100); 303(MH^+ , 13); 212(19); 169(100).

EXAMPLE 110

25

N⁴-Benzyloxycarbonyl-N¹-(tert-butoxycarbonyl)-2,2-difluoro-3-hydroxy-1,4-pentanediamine

30 The title compound was prepared in 53% yield from the amide of Example 109 by the procedure described in Example 3.

Rf: 0.47 (silica gel; ethyl acetate/cyclohexane 1:1)

MS(DCI/CI + NH_3): 406(MNH^+ , 94); 389(MH^+ , 23); 298(20); 255(100).

35

EXAMPLE 11140 N⁴-Benzyloxycarbonyl-5-cyclohexyl-2,2-difluoro-3-hydroxy-N¹-(3-methylbutanoyl)-1,4-pentanediamine

The title compound was prepared in 60% yield from isovaleric acid and the amine of Example 100 by the procedure described in Example 5.

Rf: 0.34 (silica gel; ethyl acetate/cyclohexane 1:1)

45 MS(DCI/CI + NH_3): 472(MNH^+ , 63); 455(MH^+ , 34); 321(100).

EXAMPLE 112

50

5-Cyclohexyl-2,2-difluoro-3-hydroxy-N¹-(3-methylbutanoyl)-1,4-pentanediamine

The title compound was prepared in 69% yield from the carbamate of Example 111 by the procedure described in Example 6.

55

EXAMPLE 113

N⁴-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-5-cyclohexyl-2,2-difluoro-3-hydroxy-N¹-(3-methylbutanoyl)-1,4-pentanediamine

The title compound was prepared in 78% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 112 by the procedure described in Example 5.

Rf: 0.18 (silica gel; ethyl acetate/cyclohexane 1:1)

MS(DCI/Cl + :NH₃): 684(MNH⁺, 29); 667(MH⁺, 100);

EXAMPLE 114

N⁴-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-5-cyclohexyl-2,2-difluoro-N¹-(3-methylbutanoyl)-3-oxo-1,4-pentanediamine

The title compound was prepared in 74% yield from the alcohol of Example 113 by the procedure described in Example 8.

Rf: 0.41 (silica gel; ethyl acetate/cyclohexane 1:1)

MS(DCI/Cl + :NH₃): 682(MNH⁺, 5); 665(MH⁺, 18); 364(100)

Analysis calculated for C ₃₅ H ₅₄ N ₄ O ₆ F ₂ :						
	C%:	63.23;	H%:	8.19;	N%:	8.43.
Found:	C%:	62.78;	H%:	8.27;	N%:	8.12.

EXAMPLE 115

N⁴-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-N¹-[2-(2-methylpropyl)-5-phenylpentanoyl]-1,4-heptanediamine

The title compound was prepared in 54% yield from 2-(2-methylpropyl)-5-phenylpentanoyl chloride and the amine of Example 4 by the procedure described in Example 17.

MS(DCI/Cl + :NH₃): 564(MNH⁺, 40); 547(MH⁺, 30); 413(100).

EXAMPLE 116

2,2-Difluoro-3-hydroxy-6-methyl-N¹-[2-(2-methylpropyl)-5-phenylpentanoyl]-1,4-heptanediamine

The title compound was prepared in 87% yield from the carbamate of Example 115 by the procedure described in Example 6.

MS(DCI/Cl + :NH₃): 413(MH⁺).

EXAMPLE 117

N⁴-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-N¹-[2-(2-methylpropyl)-5-phenylpentanoyl]-1,4-heptanediamine

The title compound was prepared in 26% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 116 by the procedure described in Example 5.

Rf: 0.61 (silica gel; chloroform/methanol 92:8)

MS(DCI/Cl + NH₃): 776(MNH⁺, 65); 759(MH⁺, 89); 282(85); 265(100).

EXAMPLE 118

N⁴-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-N¹-[2-(2-methylpropyl)-5-phenylpentanoyl]-3-oxo-1,4-heptanediamine

The title compound was prepared in 62% yield from the alcohol of Example 117 by the procedure described in Example 8.

Rf: 0.50 (silica gel; ethyl acetate/cyclohexane 1:1)

Analysis calculated for C ₄₂ H ₅₂ N ₄ O ₆ F ₂ :						
	C%:	66.64;	H%:	8.25;	N%:	7.40.
Found:	C%:	66.62;	H%:	8.52;	N%:	6.86.

EXAMPLE 119

N-Benzoyloxycarbonyl-4-nitrophenylalanine, methyl ester

To a mixture of N-benzyloxycarbonyl-4-nitrophenylalanine (0.3 g, 0.9 mmol) in ethyl acetate (10 mL) was added at 0 °C, a 0.5M solution of diazomethane in diethyl ether until persistence of a yellow color. The mixture was stirred for 0.5 hour at 0 °C. Acetic acid was added to destroy the excess of diazomethane (disappearance of the yellow color). Removal of the solvent in vacuo and purification of the crude product by chromatography (silica gel; ethyl acetate/cyclohexane 2:8) yielded 0.219 g of the title compound (70% yield).

Rf: 0.38 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 120

N-Benzoyloxycarbonyl-4-nitrophenylalaninal

To a suspension of N-benzyloxycarbonyl-4-nitrophenylalanine methyl ester (2.55 g, 7.1 mmol) in a mixture of toluene and diethyl ether (60 mL, 5:1), was added dropwise at -78 °C, under nitrogen, a solution of DIBAL in toluene (1M, 14.3 mL). The mixture was stirred at -78 °C for 30 min. Methanol (5 mL) and a saturated aqueous solution of Rochelle's salt (30 mL) were added and the mixture was extracted with diethyl ether (2 x 100 mL). The combined organic layers were dried over anhydrous magnesium sulphate. Filtration, removal of the solvent in vacuo, and chromatography (silica gel, ethyl acetate/n hexane 2:8) yielded 1.709 g of the title compound (73% yield).

Rf: 0.18 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 121

5 4-Benzoyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)pentanoic acid, ethyl ester

The title compound was prepared in 30% yield from the aldehyde of Example 120, ethyl bromodifluoroacetate and zinc, by the procedure described in Example 1.
 MS(DCl/Cl + iNH₃): 470(MNH₄⁺, 100); 453(MH⁺, 5).

10

EXAMPLE 122

15

4-Benzoyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)pentanamide

The title compound was prepared in 70% yield from the ester of Example 121 by the procedure described in Example 2.

20

EXAMPLE 123

25

N⁴-Benzoyloxycarbonyl-N¹-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)-1,4-pentanediamine

The title compound was prepared from the amide of Example 122 by the procedure described in Example 3.

30

EXAMPLE 124

35

N⁴-Benzoyloxycarbonyl-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)-1,4-pentanediamine

The title compound was prepared from the carbamate of Example 123 by the procedure described in Example 77.

40

EXAMPLE 125

45

N¹-Acetyl-N⁴-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)-1,4-pentanediamine

The title compound was prepared from the amine of Example 124 and acetic anhydride by the procedure described in Example 17.

50

EXAMPLE 126

55

N¹-Acetyl-N⁴-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-(4-aminophenyl)-1,4-pentanediamine

A mixture of N¹-acetyl-N⁴-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)-1,4-pen-

tanediamine (0.451 g, 1 mmol) and tin dichloride, 2 H₂O (1.128 g, 5 mmol) in absolute ethanol (5 mL) was heated at reflux under nitrogen for 1 hour. The mixture was allowed to cool to room temperature and was poured into ice. The pH was made slightly basic (pH 7-8) by addition of aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, treated with charcoal and dried over anhydrous magnesium sulphate. Filtration and removal of the solvent in vacuo yielded the title compound.

EXAMPLE 127

N¹-Acetyl-N⁴-benzyloxycarbonyl-5-(4-tert-butoxycarbonylamino)phenyl)-2,2-difluoro-3-hydroxy-1,4-pentanediamine

A solution of amine of Example 126 (0.214 g, 0.5 mmol) and di-tert-butylidicarbonate (0.131 g, 0.6 mmol) in tetrahydrofuran (10 mL) was heated at reflux for 15 hours, under nitrogen. Removal of the solvent in vacuo and chromatography (silica gel, ethyl acetate/cyclohexane 1:1) yielded the expected carbamate.

EXAMPLE 128

N¹-Acetyl-5-(4-tert-butoxycarbonylamino)phenyl)-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared from carbamate of Example 127 by the procedure described in Example 6.

EXAMPLE 129

-Acetyl-N⁴-benzoyl-5-(4-tert-butoxycarbonylamino)phenyl)-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared from the amine of Example 128 and benzoyl chloride by the procedure described in Example 17.

EXAMPLE 130

N¹-Acetyl-N⁴-benzoyl-5-(4-tert-butoxycarbonylamino)phenyl)-2,2-difluoro-3-oxo-1,4-pentanediamine

The title compound was prepared from the alcohol of Example 129 by the procedure described in Example 8.

EXAMPLE 131

N¹-Acetyl-5-(4-aminophenyl)N⁴-benzoyl-2,2-difluoro-3-oxo-1,4-pentanediamine

The title compound was prepared from the carbamate of Example 130 by the procedure described in Example 77.

EXAMPLE 132

5 N¹-Acetyl-N⁴-benzoyl-5-[4-[N¹, N¹'-bis(tert-butoxycarbonyl)-guanidino]phenyl]-2,2-difluoro-3-oxo-1,4-pentanediamine

10 A mixture of N¹-acetyl-5-(4-aminophenyl)-N⁴-benzoyl-2,2-difluoro-3-oxo-1,4-pentanediamine (0.195 g, 0.5 mmol) and N,N'-bis(tert-butoxycarbonyl)-S-methylisothiourea (0.174 g, 0.6 mmol) in tetrahydrofuran (10 mL) was heated at 55 °C for 15 hours. Removal of the solvent in vacuo left a solid residue. The residue was treated with 5% sodium bicarbonate and extracted with chloroform (2 x 20 mL). The combined organic layers were washed with water and the product was purified by chromatography (silica gel, chloroform/methanol 2:98) to yield the title compound.

EXAMPLE 133

20 N¹-Acetyl-N⁴-benzoyl-5-(4-guanidinophenyl)-2,2-difluoro-3-oxo-1,4-pentanediamine, bistrifluoroacetate

The title compound was prepared from the carbamate of Example 132 by the procedure described in Example 4.

EXAMPLE 134

30 ε-N-Benzoyloxycarbonyl-α-N-4-nitrobenzyloxycarbonyllysine

To a solution of ε-N-benzyloxycarbonyllysine (2.80 g, 10 mmol) in a mixture of tetrahydrofuran (25 mL) and 0.5N sodium hydroxide (50 mL) was added dropwise, at 0 °C, a solution of 4-nitro-benzylchloroformate (2.695 g) in tetrahydrofuran (25 mL). After completion of the addition, the temperature was allowed to rise to room temperature, and the mixture was stirred for 2 hours at that temperature. The mixture was diluted with water and washed with diethyl ether (2 x 50 mL). The aqueous phase was acidified (pH 2) and extracted with chloroform (3 x 80 mL). The combined organic extracts were dried over anhydrous magnesium sulphate. Filtration and removal of the solvent in vacuo yielded 4.042 g of the title compound (88% yield).
Rf: 0.85 (silica gel; AcOH/BuOH/H₂O 2:6:2).

40 MS(DCI/Cl⁺/NH₃): 477(MNH⁺₄, 80); 460(MH⁺, 15); 324(18); 281(25); 250(20); 237(52); 235(100); 218(45).

EXAMPLE 135

45 ε-N-Benzoyloxycarbonyl-α-N-4-nitrobenzyloxycarbonyllysine, methyl ester

The title compound was prepared in 90% yield from the acid of Example 134 by the procedure described in Example 119.

m.p.: 74-75 °C

Rf: 0.19 (silica gel; ethyl acetate/cyclohexane 1:1)

MS(DCI/Cl⁺/NH₃): 491(MNH⁺₄, 44); 474(MH⁺, 7); 295(100).

EXAMPLE 136

ϵ -N-Benzoyloxycarbonyl- α -N-4-nitrobenzyloxycarbonyllysinal

The title compound was prepared in 76% yield from the ester of Example 135 by the procedure described in Example 120.

5 Rf: 0.11 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 1378-Benzoyloxycarbonylamino-2,2-difluoro-3-hydroxy-4-(4-nitrobenzyloxycarbonylamino)-octanoic acid, ethyl ester

10 The title compound was prepared in 30% yield from the aldehyde of Example 136 by the procedure described in Example 1.

Rf: 0.56 (silica gel; ethyl acetate).

MS(DCI/CI + NH_3): 585(MNH_4^+ , 100); 568(MH^+ , 19); 450(23); 389(65); 255(45); 235(63).

EXAMPLE 1388-Benzoyloxycarbonylamino-2,2-difluoro-3-hydroxy-4-(4-nitrobenzyloxycarbonylamino)-octanamide

25 The title compound was prepared in quantitative yield from the ester of Example 137 by the procedure described in Example 2.

Rf: 0.25 (silica gel; ethyl acetate)

30 MS(DCI/CI + NH_3): 556(MNH_4^+ , 54); 539(MH^+ , 4); 421(13); 403(46); 360(41); 139(38); 106(100).

EXAMPLE 139 N^8 -Benzoyloxycarbonyl- N^1 -(tert-butoxycarbonyl)-2,2-difluoro-3-hydroxy- N^4 -(4-nitrobenzyloxycarbonyl)-1,4,8-octanetriamine

40 The title compound was prepared in 32% yield from the amide of Example 138 by the procedure described in Example 3.

MS(DCI/CI + NH_3): 642(MNH_4^+ , 100); 625(MH^+ , 10); 525(20); 507(20); 490(6); 446(28); 312(45).

EXAMPLE 140 N^8 -Benzoyloxycarbonyl-2,2-difluoro-3-hydroxy- N^4 -(4-nitrobenzyloxycarbonyl)-1,4,8-octanetriamine

50 The title compound was prepared from the carbamate of Example 139 by the procedure described in Example 77.

EXAMPLE 141

N¹-Acetyl-N⁸-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N⁴-(4-nitrobenzyloxycarbonyl)-1,4,8-octanetriamine

The title compound was prepared from the amine of Example 140 by the procedure described in Example 17.

EXAMPLE 142N¹-Acetyl-N⁸-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-1,4,8-octanetriamine

A mixture of N¹-acetyl-N⁸-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N⁴-(4-nitrobenzyloxycarbonyl)-1,4,8-octanetriamine (0.273 g, 0.5 mmol) and tin dichloride, 2 H₂O (0.564 g, 2.5 mmol) in absolute ethanol (5 mL) was heated at reflux under nitrogen for 1 hour. The mixture was allowed to cool to room temperature and was poured into ice. The pH was made basic (9-10) and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, treated with charcoal and dried over anhydrous magnesium sulphate. Filtration and removal of the solvent in vacuo yielded the title compound.

EXAMPLE 143N¹-Acetyl-N⁸-benzyloxycarbonyl-N⁴-[N-(tert-butoxycarbonyl)-D-phenylalanyl-L-prolyl]-2,2-difluoro-3-hydroxy-1,4,8-octanetriamine

The title compound was prepared from the amine of Example 142 and N-(tert-butoxycarbonyl)-D-phenylalanylproline by the procedure described in Example 5.

EXAMPLE 144N¹-Acetyl-N⁴-[N-(tert-butoxycarbonyl)-D-phenylalanyl-L-prolyl]-2,2-difluoro-3-hydroxy-1,4,8-octanetriamine

The title compound was prepared from the carbamate of Example 143 by the procedure described in Example 6.

EXAMPLE 145N¹-Acetyl-N⁸-(tert-butoxycarbonyl)-N⁴-[N-(tert-butoxycarbonyl)-D-phenylalanyl-L-prolyl]-2,2-difluoro-3-hydroxy-1,4,8-octane-triamine

The title compound was prepared from the amine of Example 144 and di-tert-butylidicarbonate by the procedure described in Example 127.

EXAMPLE 146N¹-Acetyl-N⁸-(tert-butoxycarbonyl)-N⁴-[N-(tert-butoxycarbonyl)-D-phenylalanyl-L-prolyl]-2,2-difluoro-3-oxo-1,4,8-octanetriamine

The title compound was prepared from the alcohol of Example 145 by the procedure described in Example 8.

EXAMPLE 147

N¹-Acetyl-N⁴-(D-phenylalanyl-L-prolyl)-2,2-difluoro-3-oxo-1,4,8-octanetriamine, bishydrochloride

The title compound was prepared from the ketone of Example 146 by the procedure described in Example 64.

The foregoing describes in detail the generic and specific aspects of the scope of the invention as well as the manner of making and using the invention. In addition thereto, although such procedures are known in the art, references setting forth state of the art procedures by which the compounds may be evaluated for their biochemical effects are also included herein.

For example, human elastase is assayed *in vitro* using chromophoric peptides, succinylalanylalanylalanyl-p-nitroanilide (A1), methoxysuccinylalanylalanylprolylvalyl-p-nitroanilide (A2), and others, all of which are available commercially. The assay buffer, pH 8.0, and assay techniques are similar to those described by Lottenberg, et al. (A3,A4). Enzyme is purified from human sputum (A5), although recently it has become commercially available. Kinetic characterization of immediate inhibitors is by means of the Dixon plot (A6), whereas the characterization of slow- and/or tight-binding inhibitors used data analysis techniques reviewed by Williams and Morrison (A7).

Similarly, the other proteases are assayed and effects of inhibitors are assessed *in vitro* by similar spectroscopic techniques: cathepsin G (A2); thrombin (A3); chymotrypsin (A8); trypsin (A9); plasmin (A3); C1 esterase (A10); urokinase (A3); plasminogen activator (A11); acrosin (A12); betalactamase (A13); cathepsin B (A14); pepsin (A15); cathepsin D (A16) and leucine aminopeptidase (A17). Pseudomonas elastase was measured in a coupled assay procedure using a human elastase substrate and microsomal aminopeptidase.

Radiometric assays of angiotensin I-converting enzyme and enkephalinase and their inhibitors were based on the procedure of Ryan (A18) and used tritiated substrates purchased from Ventrex Laboratories, Inc. Radioimmunoassay was used for studies with renin (A19). C3-convertase was measured as described by Tack, et al. (A20).

The individual assay references are elaborated upon by the following:

- A1. The synthesis and analytical use of a highly sensitive and convenient substrate of elastase. J. Bieth, B. Spiess and C.G. Wermuth, *Biochemical Medicine*, 11 (1974)350-375.
- A2. Mapping the extended substrate binding site of cathepsin G and human leukocyte elastase. Studies with peptide substrates related to the alpha 1-protease inhibitor reactive site. K. Nakajima, J.C. Powers, B.M. Ashe and M. Zimmerman, *The Journal of Biological Chemistry*, 254(1979)4027-4032.
- A3. Assay of coagulation proteases using peptide chromogenic and fluorogenic substrates. R. Lottenberg, U. Christensen, C.M. Jackson and P.L. Coleman, in *Methods in Enzymology*(L. Lorand, ed), Academic Press, New York, 1979, vol. 80, pp. 341-361.
- A4. Solution composition dependent variation in extinction coefficients for p-nitroaniline. R. Lottenberg and C.M. Jackson, *Biochimica et Biophysica Acta*, 742 (1983) 558-564.
- A5. A rapid procedure for the large scale purification of elastase and cathepsin G from human sputum. R.R. Martodam, R.J. Baugh, D.Y. Twumasi and I.E. Liener, *Preparative Biochemistry*, 9 (1979) 15-31.
- A6. The determination of enzyme inhibitor constants, M. Dixon, *The Biochemical Journal* 55 (1953) 170-171.
- A7. The kinetics of reversible tight-binding inhibition. J.W. Williams and J.F. Morrison, in *Methods in Enzymology* (D.L. Purich, ed), Academic Press, New York, 1979, vol. 63, pp. 437-467.
- A8. Two convenient spectrophotometric enzyme assays. A biochemistry experiment in kinetics. J.A. Hurlbut, T.N. Ball, H.C. Pound and J.L. Graves, *Journal of Chemical Education*, 50(1973) 149-151.
- A9. The preparation and properties of two new chromogenic substrates of trypsin. B.F. Erlanger, N. Kokowsky and W. Cohen, *Archives of Biochemistry and Biophysics*, 95 (1961) 271-278.
- A10. The human complement system serine proteases C1r and C1s and their proenzymes. R.B. Sim, in *Methods in Enzymology* (L. Lorand, ed), Academic Press, New York, 1979, vol. 80, pp. 26-42.
- A11. Extrinsic plasminogen activator and urokinase. J.H. Verheijen, C. Kluft, G.T.G. Chang and E.

Mullaart, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 425-433.

A12. Sperm acrosin. W. Mueller-Esterl and H. Fritz, in *Methods in Enzymology* (L. Lorand, ed), Academic Press, New York, 1979, vol. 80, pp. 621-632.

A13. Novel method for detection of beta-lactamases by using a chromogenic cephalosporin substrate. C.H. O'Callaghan, A. Morris, S.M. Kirby and A.H. Shingler, *Antimicrobial Agents and Chemotherapy*, 1 (1972) 283-288.

A14. Cathepsin B, cathepsin H. and cathepsin L. A.J. Barrett and H. Kirschke, in *Methods in Enzymology* (L. Lorand, ed), Academic Press, New York, 1979, vol. 80, pp. 535-561.

A15. Pepsins, gastricsins and their zymogens. A.P. Ryle, in *Method of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 223-238.

A16. Cathepsin D, cathepsin E. V. Turk, T. Lah and I. Kregar, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 211-222.

A17. Amino acid arylamidase. J.C.M. Hafkenscheid, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 11-15.

A18. Angiotensin I converting enzyme (kininase II). J.W. Ryan, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 20-34.

A19. Renin. T. Inagami and M. Naruse, in *Methods of Enzymatic Analysis* (H.U. Bergmeyer, J. Bergmeyer and M. Grassl, eds), Verlag Chemie, Weinheim, 1984, third edition, vol. 5, pp. 249-258.

A20. The third, fourth, and fifth components of human complement: isolation and biochemical properties. B.F. Tack, J. Janatova, M.L. Thomas, R.A. Harrison and C.H. Hammer, in *Methods in Enzymology* (L. Lorand, ed), Academic Press, New York, 1979, vol. 87, pp. 64-101.

By following the techniques referenced above, as well as by utilization of other known techniques, as well as by comparison with compounds known to be useful for treatment of the above-mentioned disease states, it is believed that adequate material is available to enable one of ordinary skill in the art to practice the invention. Of course, in the end-use application of the compounds of this invention, the compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules or elixers, for oral administration or in sterile solutions or suspensions for parenteral administration. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in a dosage range of 5 to 500 mg per patient generally given several times, thus giving a total daily dose of from 5 to 2000 mg per day. As stated above, the dose will vary depending on severity of disease, weight of patient and other factors which a person skilled in the art will recognize.

Typically the compounds described above are formulated into pharmaceutical compositions as discussed below.

About 10 to 500 mg of a compound or mixture of compounds of formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type, a liquid carrier such as fatty oil.

Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

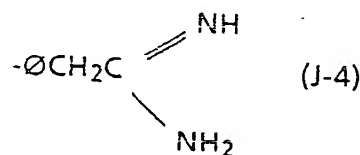
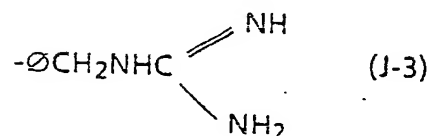
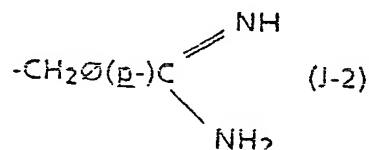
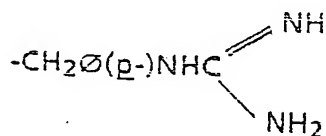
Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

While the invention has been described in connection with specific embodiments thereof, it will be

understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows

Claims

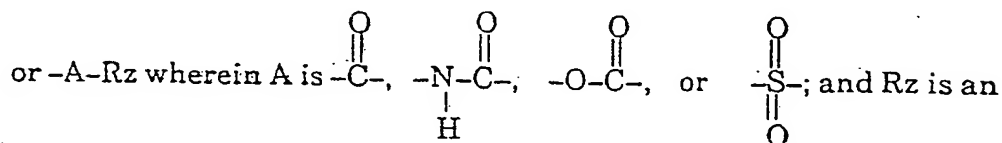
1. A compound of the formula
 $R_1NHCHR_2COCF_2CHR_3(NR_bCOXR_a)_nQ$
 the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein
 R_1 is hydrogen, an amino protecting group selected from Group K, an α -amino acid or a peptide comprised of a number of α -amino acid building blocks, each of said α -amino acid or peptide optionally bearing an amino protecting group preferably selected from Group K,
 R_2 is a specific characteristic "R group" side chain of the α -amino acid building block responsible for directing the inhibitor to the active site of the enzyme,
 R_3 is H, C_{1-6} straight or branched alkyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl, or is the R-group residue of an α -amino acid building block for that peptidase substrate analog,
 n is an integer of 1 to 10,
 R_a is a specific characteristic "R-group" side chain of an α -amino acid building block for that peptidase substrate analog, or is an ethylene moiety which when attached to the N atom of that retroamide moiety forms a 2-oxopyrrolidine moiety,
 R_b is H, C_{1-6} straight or branched alkyl, or an ethylene moiety which when linked to the CH moiety of X forms a 2-oxopyrrolidine moiety,
 X is H, CH, OR_7 or R_7 with R_7 being C_{1-6} straight or branched alkyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl with the proviso that when X is other than CH, R_a and Q are deleted,
 Q is H, C_{1-10} alkyl or arylalkyl, COR_5Y , or COY with R_5 being an α -amino acid R-group or a peptide comprised of α -amino acid building blocks,
 Y is NHR_4 or OR_4 , with R_4 being H, C_{1-6} straight or branched alkyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl, wherein the said α -amino acid and peptide moieties are building blocks selected from Groups A, B, C, D, E, F, G and J, and K is a terminal amino protecting group, members of these groups being
 Group A: Lys and Arg
 B: Ser, Thr, Gln, Asn, Cys, His, and N-methyl derivatives
 D: Pro, Ind
 E: Ala, Leu, Ile, Val, η -Val, Met, β -Val, β -Ala, η -Leu and N-methyl derivatives
 F: Phe, Tyr, O-methyl Tyrosine, Trp, Nal(1), and N-methyl derivatives
 G: Gly, Sar
 J:
 K:



with ϕ , of course, representing phenyl (it being understood that the bond of J1-4 is always attached to an amino acid),

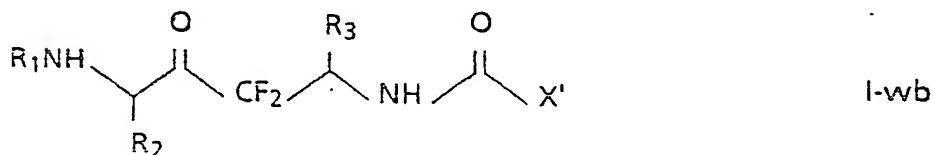
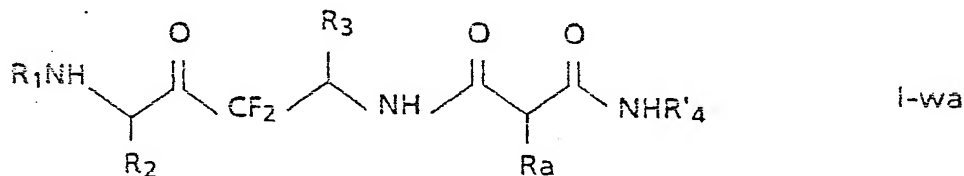
K: Acetyl (Ac), Succinyl(Suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxo (CBZ), Tosyl

(Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantenesulphonyl (AdSO₂), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), phenylacetyl (cobenzyl), tert-butylacetyl (Tba), bis[1-naphthyl)methyl]acetyl(BNMA)



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aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylaminocarbonyl) containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and such other terminal amino protecting groups which are functionally equivalent thereto.

2. A compound of Claim 1 useful for inhibiting retroviral proteases having the formulae



R₁ is P₂, P₃, P₄ with

40 P₂ is selected from Groups C', E', F' and G',

P₃ is selected from Groups C', E', F' and G',

P₄ is selected from Group C' or β-Ala or β-Val, which may optionally bear an amino protecting group selected from Group K,

R₂ is a residue of the P₁-position α-amino acid of Groups F', E', CHM,

45 R₃ is Gly or Group E',

R₄ is H, C₁₋₆ alkyl, aralkyl,

R_a is a residue of the P₂-position α-amino acid of Group E' or Val,

X' is H or R₇.

3. A compound of Claim 2 selected from the group consisting of

50 Ser-Gln-Asn-Tyr[CF₂GlyNH]_m-LeuNH₂,

Thr-Gln-Asn-Tyr[CF₂GlyNH]_m-LeuNHCHM,

Ser-Gln-Asn-Tyr[CF₂GlyNH]C(O)H,

Ser-Gln-Asn-Tyr[CF₂GlyNH]C(O)CHM,

β-Ala-(O-Me)-Tyr-n-Val-"CHM"-[CF₂GlyNH]Iva,

55 Boc-Phe-n-Val-"CHM"-[CF₂GlyNH]Iva,

Iva-Ser-Gln-Asn-Tyr-[CF₂IleNH]Iva,

Iva-Ser-Phe-n-Val-"CHM"-[CF₂GlyNH]Iva,

Iva-Ser-Gln-Asn-Phe-[CF₂GlyNH]_mValNH₂ and

Iva-Ser-Gln-Asn-Tyr-[CF₂IleNH]mValNH₂.

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	BIOLOGICAL ABSTRACTS, vol. 86, 1988, abstract no. 86065299, Philadelphia, PA., US; M. KOTLER et al.: "Synthetic peptides as substrates and inhibitors of a retroviral protease", & PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA(US) 1988, vol. 85, no. 12, p4185-4189 * Abstract * -----	1-3	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 27-03-1989	Examiner MASTURZO P.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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EUROPEAN SEARCH REPORT

Application Number

EP 88 40 2205

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X,Y	EP-A-0 275 101 (MERRELL DOW) * Whole document *	1-3	C 07 K 5/02 C 07 K 5/06
Y	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 85, no. 18, September 1988, pages 6612-6616; S. SEELMEIER et al.: "Human immunodeficiency virus has an aspartic-type protease that can be inhibited by pepstatin A" * Whole article *	1-3	C 07 K 5/08 C 07 K 5/10 A 61 K 37/00
Y	CHEMICAL ABSTRACTS, vol. 107, no. 23, 7th December 1987, page 274, abstract no. 214141y, Columbus, Ohio, US; L.H. PEARL et al.: "A structural model for the retroviral proteases", & NATURE (LONDON) 1987, 329(6137), 351-4 * Abstract *	1-3	
Y	CHEMICAL ABSTRACTS, vol. 107, no. 25, 21st December 1987, page 368, abstract no. 231968r, Columbus, Ohio, US; I. KATOH et al.: "Inhibition of retroviral protease activity by an aspartyl proteinase inhibitor", & NATURE (LONDON) 1987, 329(6140), 654-6 * Abstract *	1-3	TECHNICAL FIELDS SEARCHED (Int. Cl. 4) C 07 K A 61 K
A	EP-A-0 187 721 (DU PONT DE NEMOURS) * Pages 36-37, claims 1-7 *	1-3	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 27-03-1989	Examiner MASTURZO P.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier parent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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